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(54) Title: COMBINATIONS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ALPHA AGONISTS AND CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AND THERAPEUTIC USES THEREFOR

(57) Abstract: Methods for the treatment, prevention, or inhibition of pain, inflammation, or inflammation-related disorder, and for the treatment or inhibition of cardiovascular disease or disorder, and for the treatment or inhibition of cancer, and for the treatment of Alzheimer's disease in a subject in need of such treatment, prevention, or inhibition, include treating the subject with a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof. Compositions, pharmaceutical compositions and kits for effecting the particular methods are also described.

COMBINATIONS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-ALPHA AGONISTS AND CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AND THERAPEUTIC USES THEREFOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is related to, and claims priority to, U.S. Provisional Patent Application Serial No. 60/348,297, filed January 14, 2002, which is hereby incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates to compositions that include peroxisome proliferator-activated receptor agonists and cyclooxygenase-2 selective inhibitors, and more particularly to compositions that include a combination of a peroxisome proliferator-activated receptor alpha agonist and an cyclooxygenase-2 selective inhibitor and their use for the treatment, prevention, or inhibition of cancer, cardiovascular/metabolic disease or disorder, Alzheimer's disease, and pain, inflammation, or inflammation-related disorder.

(2) Description of the Related Art:

[0003] Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor superfamily of ligand-activated transcription factors. Once bound by a ligand, PPARs heterodimerize with 9-cis retinoic acid receptors (RXRs) in the nucleus. These heterodimers bind to specific peroxisome-proliferator response elements (PPRE) in the promoter of target genes, thereby regulating transcription and expression of these genes. Three isoforms of PPARs, alpha, delta, and gamma, have been identified and differ in their tissue distribution, affinity for particular ligands, and physiological consequences. See, *e.g.*, Corton, J.C. *et al.*, *Annu. Rev. Pharmacol. Toxicol.*, 40:491-518 (2000), and Chawla, A. *et al., Science, 294*:1866 - 1870 (2001).

[0004] One of the first PPARs identified was PPAR alpha (PPARα), which is activated by binding with such compounds as fibrates, fibric acid

derivatives and long-chain fatty acids. See, *e.g.,* Staels, B. *et al., Circulation, 98(19)*:2088-93 (1998). Activation of PPARα by ligand binding results in changes in the expression of genes important in lipid biooxidation. Fruchart, J.C. *et al.,* in *Curr. Opin. Lipidol., 10(3)*:245-57 (1999), report that PPARα activation mediates pleiotropic effects such as stimulation of lipid oxidation, alteration in lipoprotein metabolism and inhibition of vascular inflammation. PPARα activators increase helatic uptake and the esterification of free fatty acits by stimulating the fatty acid transport protein and acyl-CoA synthetase expression. In skeletal muscle and heart, PPARα increases mitochondrial free fatty acide uptake and the resulting free fatty acid oxidation through stimulating the muscle-type carnitine palmitoyltransferase-1.

[0005] For further information about the activity of PPARs in general and PPARα in particular, see, *e.g.*, Schoonjans, K. *et al., Biochim. Biophys. Acta, 1302(2)*:93-109 (1996); Kersten, S. *et al, EXS, 89*:141-51 (2000); and Hertz, R. *et al., Toxicol. Lett., 102-103*:85-90 (1998).

[0006] As a consequence of these changes in gene expression, compounds such as fibrates act as PPARα ligands to regulate lipid metabolism, and fenofibrate -- as an example -- has been approved for the management of hypercholersterolemia and hypertriglyceridemia. See, *e.g., TRICOR®*, Prescribing information #011-030-0565-1, August 2001, Abbott Laboratories, North Chicago, IL 60064, .

[0007] Ligands that cause some physiological consequence by binding with a receptor can be referred to as agonists. Emerging evidence indicates that PPARα agonists have potential clinical uses beyond treatment of hyperlipidemia and hypertriglyceridemia. For example, Seedorf, U. *et al, Nutr. Metab. Cardiovasc. Dis., 11(3)*:189-94 (2001), describe the function of PPARα in potential Syndrome X therapy; Robins, S. J., *J. of Cardiovascular Risk, 8(4)*:195 - 201 (2001), and Marx, N., *et al., J. of Cardiovascular Risk, 8(4)*:203-210 (2001), report that PPARα ligands may reduce cardiovascular risk; Barger, P.M. *et al., J. Biol. Chem., Sep.*

27 (2001), discuss the role of PPARα in managing the cardiac metabolic stress response; Plutzky, J., *Curr. Opin. Lipidol., 12(5)*:511-8 (2001), and Duez, H, *et al., J. Cardiovascular Risk, 8*:187 - 194 (2001), discuss the role of fibrates in altering the process of atherosclerosis; Michalik, L. *et al., J. Cell. Biol., 154(4)*:799-814 (2001), describe the role of PPARα in rapid epithelialization of a skin wound; Vanden Heuvel, J.P., *Toxicol. Sci., 47(1)*:1 - 8 (1999), and James, N.H. *et al., Toxicol. Lett., 102-103*:91-96 (1998), discuss the involvement of PPARα in carcinogenesis and hepatocarcinogenesis.

[0008] Recent work has shown promising results that PPARα may protect against Alzheimer's disease (See, in't Veld, B. A., *et al., The New England J. of Med., 345(21)*:1515- 1521 (2001)), and serve to regulate beta-amyloid stimulated proinflammatory responses (See, Combs, C. K. *et al., Neuorchem Int., 39(5-6)*:449 - 457 (2001)).

[0009] As work has progressed on the elucidation of biological activities of PPARα in lipid metabolism, research in the area of arachidonic acid metabolism has resulted in the discovery of compounds that selectively inhibit the cyclooxygenase-2 enzyme. These compounds selectively inhibit the activity of Cox-2 to a greater extent than the activity of Cox-1. The new Cox-2-selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, cyclooxygenase-2-selective inhibitors have shown great promise for use in therapies -- especially in therapies that require extended administration, such as for pain and inflammation control for arthritis. Additional information on the identification of cyclooxygenase-2-selective inhibitors can be found in: (1) Buttgereit, F. *et al., Am. J. Med., 110(3 Suppl. 1)*:13-9 (2001); (2) Osiri, M. *et al, Arthritis Care Res., 12(5)*:351-62 (1999); (3) Buttar, N.S. *et al., Mayo Clin. Proc., 75(10)*:1027-38 (2000); (4) Wollheim, F. A., *Current Opin. Rheumatol., 13*:193-201 (2001); (5) U.S. Patent Nos. 5,434,178 (1,3,5-trisubstituted pyrazole compounds); (6) 5,476,944

(derivatives of cyclic phenolic thioethers); (7) 5,643,933 (substituted sulfonylphenylheterocycles); 5,859,257 (isoxazole compounds); (8) 5,932,598 (prodrugs of benzenesulfonamide-containing Cox-2 inhibitors); (9) 6,156,781 (substituted pyrazolyl benzenesulfonamides); and (10) 6,110,960 (for dihydrobenzopyran and related compounds).

[00010] The efficacy and side effects of cyclooxygenase-2-selective inhibitors for the treatment of inflammation have been reported. References include: Hillson, J. L. *et al., Expert Opin. Pharmacother., 1(5)*:1053-66 (2000), (for rofecoxib, Vioxx®, Merck & Co., Inc.); Everts, B. *et al., Clin. Rheumatol., 19(5)*:331-43 (2000), (for celecoxib, Celebrex®, Pharmacia Corporation, and rofecoxib); Jamali, F., *J. Pharm. Pharm. Sci., 4(1)*:1 - 6 (2001), (for celecoxib); U.S. Patent Nos. 5,521,207 and 5,760,068 (for substituted pyrazolyl benzenesulfonamides); Davies, N. M. *et al., Clinical Genetics*, Abstr. at http://www.mmhc.com/cg/articles/CG0006/davies.html (for meloxicam, celecoxib, valdecoxib, parecoxib, deracoxib, and rofecoxib); http://www.celebrex.com (for celecoxib); http://www.docguide.com/dg.nsf/PrintPrint/F1F8DDD2D8B0094085256 98F00742187, 5/9/2001 (for etoricoxib, MK-663, Merck & Co., Inc.); Saag, K. *et al., Arch. Fam. Med., 9(10)*:1124 - 34 (2000), (for rofecoxib); International Patent Publication No. WO 00/24719 (for ABT 963, Abbott Laboratories).

[00011] Cox-2 inhibitors have also been described for the treatment of cancer (WO98/16227) and for the treatment of tumors (See, EP 927,555, and Rozic *et al., Int. J. Cancer, 93(4)*:497 - 506 (2001)). Celecoxib®, a selective inhibitor of Cox-2, exerted a potent inhibition of fibroblast growth factor-induced corneal angiogenesis in rats. (Masferrer *et al., Proc. Am. Assoc. Cancer Research 1999, 40:* 396). WO 98/41511 describes 5-(4-sulphunyl-phenyl)-pyridazinone derivatives used for treating cancer. WO 98/41516 describes (methylsulphonyl)phenyl-2-(5H)-furanone derivatives that can be used in the treatment of cancer. Kalgutkar, A. S. *et al., Curr. Drug Targets, 2(1)*:79 - 106 (2001) suggest that Cox-2 selective inhibitors

could be used to prevent or treat cancer by affecting tumor viability, growth, and metastasis. Masferrer *et al.*, in *Ann. NY Acad. Sci., 889*:84 - 86 (1999) describe Cox-2 selective inhibitors as antiangiogenic agents with potential therapeutic utility in several types of cancers. The utility of Cox-2 inhibition in clinical cancer prevention was described by Lynch, P. M., in *Oncology, 15(3)*:21 - 26 (2001), and Watanabe *et al.*, in *Biofactors 2000, 12(1 - 4)*:129 - 133 (2000) described the potential of Cox-2 selective inhibitors for chemopreventive agents against colon cancer.

[00012] Additionally, various combination therapies using Cox-2 inhibitors with other selected combination regimens for the treatment of cancer have also been reported. See *e.g.*, FR 27 71 005 (compositions containing a cyclooxygenase-2 inhibitor and N- methyl-d-aspartate (NMDA) antagonist used to treat cancer and other diseases); WO 99/18960 (combination comprising a cyclooxygenase-2 inhibitor and an induced nitric-oxide synthase inhibitor (iNOS) that can be used to treat colorectal and breast cancer); WO 99/13799 (combination of a cyclooxygenase-2 inhibitor and an opioid analgesic); WO 97/36497 (combination comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer); WO 97/29776 (composition comprising a cyclooxygenase-2 inhibitor in combination with a leukotriene B4 receptor antagonist and an immunosuppressive drug); WO 97/29775 (use of a cyclooxygenase-2 inhibitor in combination with a leukotriene A4 hydrolase inhibitor and an immunosuppressive drug); WO 97/29774 (combination of a cyclooxygenase-2 inhibitor and protstagladin or antiulcer agent useful in treating cancer); WO 97/11701 (combination comprising of a cyclooxygenase-2 inhibitor and a leukotriene B receptor antagonist useful in treating colorectal cancer); WO 96/41645 (combination comprising a cyclooxygenase-2 inhibitor and leukotriene A hydrolase inhibitor); WO 96/03385 (3,4,-Di substituted pyrazole compounds given alone or in combination with NSAIDs, steroids, 5-LO inhibitors, LTB4 antagonists, or LTA4 hydrolase inhibitors for the treatment of cancer); WO 98/47890 (substituted benzopyran derivatives that may be

used alone or in combination with other active principles); WO 00/38730 (method of using cyclooxygenase-2 inhibitor and one or more antineoplastic agents as a combination therapy in the treatment of neoplasia); Mann, M. *et al., Gastroenterology, 120(7)*:1713 - 1719 (2001) (combination treatment with Cox-2 and HER-2/neu inhibitors reduced colorectal carcinoma growth).

[00013] Other reports have indicated the Cox-2 selective inhibitors have cardiovascular applications. For example, Saito, T. *et al.,* in *Biochem. Biophys. Res. Comm., 273*:772 - 775 (2000), reported that the inhibition of Cox-2 improves cardiac function in myocardial infarction. Ridker, P.M. *et al.,* in *The New England J. of Med., 336(14)*:973 - 979 (1997), raised the possibility that anti-inflammatory agents may have clinical benefits in preventing cardiovascular disease. In addition, Cox-2 selective inhibitors have been proposed for therapeutic use in cardiovascular disease when combined with modulation of inducible nitric oxide synthase (See, Baker, C. S. R. *et al., Arterioscler. Thromb. Vasc. Biol., 19*:646-655 (1999)), and with HMG-CoA reductase inhibitor (U.S. Patent No. 6,245,797).

[00014] It would be useful, therefore, to provide an effective method for the treatment, prevention, or inhibition or pain, inflammation, or inflammation-related disorder, and also an effective method for the treatment and prevention of cancer and cardiovascular disease or disorder. It would also be useful if these methods provided beneficial properties that were not provided by known and conventional methods of treatment for these conditions.

SUMMARY OF THE INVENTION

[00015] Briefly, therefore, the present invention is directed to a novel method for the prevention, treatment, or inhibition of pain, inflammation, or inflammation-related disorder, or cancer, or Alzheimer's disease, or cardiovascular disease or disorder in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

[00016] The invention is also directed to a novel method for the treatment or prevention of disorders having an inflammatory component in a subject in need of the treatment or prevention of disorders having an inflammatory component, the method comprising administering to the subject a therapeutically effective dose of a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

[00017] The invention is also directed to a novel composition for the treatment, prevention, or inhibition or pain, inflammation, or inflammation-associated disorder comprising a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

[00018] The invention is also directed to a novel pharmaceutical composition comprising a peroxisome proliferator activated receptor-α agonist; a cyclooxygenase-2 selective inhibitor or prodrug thereof; and a pharmaceutically-acceptable excipient.

[00019] The invention is also directed to a novel kit that is suitable for use in the treatment, prevention or inhibition of pain, inflammation or inflammation-associated disorder, the kit comprises a first dosage form comprising a peroxisome proliferator activated receptor-α agonist and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the combination of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

[00020] The invention is also directed to a novel method for the treatment, prevention, or inhibition of cardiovascular disease or disorder in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator-activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

[00021] The invention is also directed to a novel composition for the treatment, prevention, or inhibition of cardiovascular disease or disorder comprising a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

[00022] The invention is also directed to a novel kit that is suitable for use in the treatment, prevention, or inhibition of cardiovascular disease or disorder, wherein the kit comprises a first dosage form comprising a peroxisome proliferator activated receptor-α agonist and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of cardiovascular disease or disorder.

[00023] The invention is also directed to a novel method for the treatment, prevention, or inhibition of cancer in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator-activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

[00024] The invention is also directed to a novel composition for the treatment, prevention, or inhibition of cancer comprising a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

[00025] The invention is also directed to a novel kit that is suitable for use in the treatment, prevention, or inhibition of cancer, wherein the kit comprises a first dosage form comprising a peroxisome proliferator activated receptor-α agonist and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of cancer.

[00026] The invention is also directed to a novel method for the prevention, treatment, or inhibition of diseases or disorders that are

mediated by the activity of PPARα in a subject that is in need of such prevention, treatment or inhibition, the method comprising administering to the subject a combination of a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof, where the amounts of the two materials together comprise an effective amount of the combination.

[00027] The invention is also directed to a novel method for the treatment, prevention, or inhibition of Alzheimer's disease in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator-activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

[00028] The invention is also directed to a novel composition for the treatment, prevention, or inhibition of Alzheimer's disease comprising a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

[00029] The invention is also directed to a novel kit that is suitable for use in the treatment, prevention, or inhibition of Alzheimer's disease, wherein the kit comprises a first dosage form comprising a peroxisome proliferator activated receptor-α agonist and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of Alzheimer's disease.

[00030] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of an effective method for the treatment, prevention, or inhibition or pain, inflammation, or inflammation-related disorder, and also an effective method for the treatment and prevention of cancer, Alzheimer's disease and cardiovascular disease or disorder, the provision of such methods that provided beneficial properties that are comparable to or superior to those

provided by known and conventional methods of treatment for these conditions, and the provision of compositions, pharmaceutical compositions and kits to effect these methods.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00031] In accordance with the present invention, it has been discovered that pain, inflammation and inflammation-associated disorders, as well as Alzheimer's disease, cardiovascular diseases and disorders, and cancer can be effectively prevented, inhibited, and/or treated in subjects that are in need of such prevention, inhibition, or treatment by treating the subject with a combination that includes a peroxisome proliferator-activated receptor-alpha (PPARα) agonist and one or more cyclooxygenase-2 selective inhibitors.

[00032] The amount of the PPARα agonist and the amount of the cyclooxygenase-2-selective inhibitor that are used in the treatment can be selected so that together they constitute a pain or inflammation suppressing treatment or prevention effective amount, or a cardiovascular disease or disorder treatment or prevention effective amount, or a cancer treatment or prevention effective amount, or an Alzheimer's disease treatment or prevention effective amount..

[00033] The novel method of treating a subject with a combination of a PPARα agonist and a cyclooxygenase-2-selective inhibitor provides a safe and efficacious method for preventing and alleviating pain and inflammation and for preventing and treating disorders that are associated with inflammation, as well as for treating and prevention cardiovascular diseases and disorders, Alzheimer's disease, and cancer. In addition to being an efficacious method and composition for preventing and/or alleviating such disorders in a treated subject, such method and composition can also provide desirable properties such as stability, ease of handling, ease of compounding, lack of side effects, ease of preparation or administration, and the like.

[00034] The novel method and compositions comprise the use of a PPARα agonist and a cyclooxygenase-2 selective inhibitor in combination.

[00035] As used herein, the terms "peroxisome proliferator activated receptor-alpha agonist", or "PPARα agonist" and "PPAR-alpha agonist" refer to a compound or composition, which when combined with PPARα, is capable of directly or indirectly stimulating or increasing an *in vivo* or *in vitro* reaction that is typical for the receptor, *e.g.*, transcriptional regulation activity. It is preferred that the PPARα agonists of the present invention are compounds that are capable of binding with PPARα as an activating ligand.

[00036] It is also preferred that the PPARα agonists that are used in the present invention are selective agonists for PPARα, relative to activation of the other PPARs, PPARγ in particular. By way of illustration, the concentration of a compound that is effective for the activation of a PPAR can be expressed in terms of its IC_{50} (*in vitro* or *ex vivo*) or ED_{50} (*in vivo*) value. The lower the ED_{50} or the IC_{50} value, the higher the activity of the compound. For purposes of this invention, a compound is understood to be a selective PPARα agonist if the IC_{50} PPARγ/ IC_{50} PPARα ratio (or the comparable ED_{50} ratio) is at least 1, where the IC_{50} or ED_{50} values for the two types of PPARs are determined under the same conditions and where such conditions are typical for assays of this type. It is preferred that the ratio be at least 10, and even more preferably at least 50.

[00037] PPARα agonists and the IC_{50} or ED_{50} values for such compounds can be identified via a variety of assays that are known to those of skill in the art, including, but not limited to, the transfection assay described in U.S. Patent No. 6,306,854; and the Gal-4 hPPAR transactivation assays described in U.S. Patent No. 6,200,998.

[00038] Examples of preferred PPARα agonists are listed in Table 1, and indications for which such agonists have been identified as being therapeutically useful are shown in Table 2.

Table 1: PPARα Agonists.

PPARα AGONIST[a]	CAS REG. NO.[b]	CHEMICAL NAME	CITATION(S)
WY-14,643	50892-23-4	[4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid	Yoshikawa, et al., Eur. J. Pharmacol., 426(3):201-6 (2001)
fenofibrate	54419-31-7		U.S. Pat. Nos. 5,830,148; 6,074,670; 5,827,536; 5,545,628; 6,277,405; Casas, F. et al., FEBS Lett., 482(1-2):71-4 (2000)
medium and long chain fatty acids; fibric acid derivatives; clofibrate, fenofibrate,	--- --- --- 637-07-0		U.S. Pat. Nos. 6,008,237; 6,200,998

benzafibrate, ciprofibrate, beclofibrate (beclobrate), etofibrate; gemfibrozil	49562-28-9 52214-84-3 --- 55937-99-0 31637-97-5 25812-30-0		
Arylthiazolidine-dione derivatives (general structure)			U.S. Pat. Nos. 6,200,998; 6,008,237
Propionic acid derivatives (general structure)			U.S. Pat. No. 6,306,854
pioglitazone	111025-46-8		Smith, U., *Int. J. Clin. Pract. Suppl., 121:*13 - 18 (2001)
benzafibrate (bezafibrate)	41859-67-0		Yoshikawa et al., Eur. J. Pharmacol., 426(3):2001-6 (2001); Bonilla, S. et al., J. Physiol. Biochem., 57(1):1-8 (2001); Pedraza, N., et al., Diabetes, 49(7):1224-30 (2000)
(-) DRF2725		(-)3-[4-[2-(phenoxazin-	Lohray, B.B. et al., J. Med. Chem., 44(15):2675-8 (2001)

		10-yl)ethoxy]phenyl]-2-ethoxypropionic acid	
BM-17.0744			Carroll, R. et al., Physiol. Heart Circ. Physiol., 281(2):H888-94 (2001)
ciprofibrate	52214-84-3		Latruffe, N. et al., Cell Biochem. Ciophys., 32 Spring:213-20 (2000)
omega-3-fatty acids (general); docosahexanoic acid			Diep, Q.H. et al., Hypertension, 36(5):851 - 5 (2000)
clofibrate	637-07-0		Mehendale, H.M., Toxicol. Sci., 57(2):187-90 (2000)
JTT-501		4-[4-[2-(5-methyl-2-phenyl]-4-oxazolyl)ethoxy)benzyl]-3,5-isoxazolidiedione	Shibata, T. et al., Br. J. Pharmacol., 30(3):495-504 (2000)
trichloroacetate; dichloroacetate; DHEA-S		--- --- dehydroepiandrosterone-3-beta-sulfate	Zhou, Y.C. et al, Environ. Health Perspect., 106(Suppl. 4):983-988 (1998)

Unsaturated C:18 fatty acids (general); arachidonic acid; leukotriene B4	--- --- ---		Lin, Q., et al., Biochemistry, 38(1):185-90 (1999)
Fibrates (general)			Staels, B. et al, Biochimie, 79(2-3):95-9 (1997)
Fatty aryls (generally)		4-iodophenylbutyrate; 4-chlorophenylbutyrate; clofibate; phenylbutyrate; naphthylacetate; 2,4-D; 4-chlorophenylacetate; phenylacetate; indoacetate	Pineau, T. et al., Biochem. Pharmacol., 53(4):659-67 (1996)
Fibrates (generally); beclobrate;			_____, Anatomical Classification Guidlines, http://www.ephmra.rog/atc/6_002C10.html, 11/19/2001.

bezafibrate; ciprofibrate; clofibrate; clofibride; etofibrate; fenofibrate; gemfibrozil; simfibrate			

Notes:

a. The common name of the compound or the developmental identigication code is given;

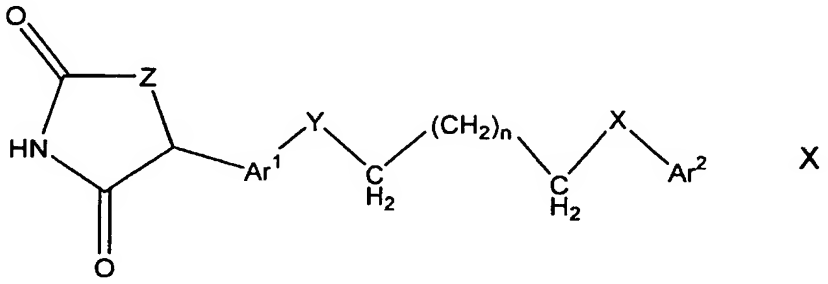
b. CAS Reg. No. means Chemical Abstracts Service Registration Number.

Table 2: Indications for the therapeutic use of PPARα agonists

INDICATIONS	CITATION(S)
Hyperglycaemia, hyperlipidaemia	Shibata, T. *et al., Br. J. Pharmacol., 30(3)*:495-504 (2000)
Atherosclerosis	Fruchart, J.C. *et al., J. Soc. Biol., 193(1)*:67-75 (1999); Plutzky, J., *Curr. Opin. Lipidol., 12(5)*:511-518 (2001)
Ischemic heart diseases	Kinoshita, M., *Nippon Rinsho, 57(12)*:2826-30 (1999)
Age-related disorders: dyslipidemia, insulin resistance, chronic inflammation, predisposition to atherosclerosis	Pineda Torra, I., *et al., Curr. Opin. Lipidol., 10(2)*:151-9 (1999)
Tumorigenesis	Vanden Heuvel, J.P., *Toxicol. Sci., 47(1)*:1 - 8 (1999)
Hepatocarcinogenesis	Peters, J.M., *et al., Carcinogenesis, 18(2)*:2029-33 (1997)
Atheromatous diseases	U.S. Patent No. 5,880,148
Diabetes mellitus, hyperglycemia, obesity, hyperlipidemia, hypertriglyceridemia, hypercholesteremia, raising HDL levels, atherosclerosis, vascular restinosis, irritable bowel syndrome, pancreatitis, abdominal obesity, adipose cell tumors, adipose cell carcinomas, liposarcoma, disorders where insulin resistance is a component, Syndrome X, ovarian hyperandrogenism.	U.S. Patent No. 6,200,998

Obesity, Syndrome X, hyperlipidemia, hypoalphalipoproteinemia, type II diabetes, atherosclerosis	Seedorf *et al., Nutr. Metab. Cardiovasc. Dis., 11(3)*:189-194 (2001)
Vascular disease	Marx, N. *et al., Z. Kardiol., 90(7)*:470-7 (2001)
Skin wound healing	Michalik, L., *et al., J. Cell. Biol., 154(4)*:799-814 (2001)
Dyslipidemia	Lohray, B.B. et al., J. Med. Chem., 44(15):2675-8 (2001)

[00039] Compounds that can act as the PPARα agonist of the present invention are described in U.S. Patent No. 6,200,998, which describes arylthiazolidinedione derivatives. The compounds are described as having the structure of formula X:



X

wherein

Ar^1 is (1) arylene or

(2) heteroarylene,

wherein arylene and heteroarylene are optionally substituted with from 1 to 4 groups selected from R^a;

Ar^2 is (1) ortho-substituted aryl or

(2) ortho-substituted heteroaryl,

wherein said ortho substituent is selected from R;

and aryl and heteroaryl are optionally further substituted with from 1 - 4 groups independently selected from R^a;

X and Y are independently O, S, N-R^b, or CH_2;

Z is O or S;

n is 0 to 3;

R is (1) C_{3-10} alkyl optionally substituted with 1 - 4 groups selected from halo and C_{3-6} cycloalkyl,

(2) C_{3-10} alkenyl, or

(3) C_{3-8} cycloalkyl;

R^a is (1) C_{1-5} alkanoyl,

(2) C_{1-5} alkyl,

(3) C_{2-15} alkenyl,

(4) C_{2-15} alkynyl,

(5) halo,
(6) OR^b,
(7) aryl, or
(8) heteroaryl,
wherein said alkyl, alkenyl, alkynyl, and alkanoyl are optionally substituted with from 1-5 groups selected from R^c, and said aryl and heteroaryl optionally substituted with 1 to 5 groups selected from R^d;

R^b is (1) hydrogen,
(2) C_{1-10} alkyl,
(3) C_{2-10} alkenyl,
(4) C_{2-10} alkynyl,
(5) aryl,
(6) heteroaryl,
(7) aryl C_{1-15} alkyl,
(8) heteroaryl C_{1-5} alkyl,
(9) C_{1-5} cycloalkyl,
(10) C_{3-8} cycloalkyl,
wherein alkyl, alkenyl, alkynyl are optionally substituted with one to four substituents independently selected from R^c, and cycloalkyl, aryl, and heteroaryl are optionally substituted with one to four substituents independently selected from R^d; or

R^c is (1) halo,
(2) aryl,
(3) heteroaryl,
(4) CN,
(5) NO_2,
(6) OR^f,
(7) $S(O)_mR^f$, m=0, 1 or 2, provided that R^f is not H when m is 1 or 2;
(8) NR^fR^f,
(9) NR^fCOR^f,
(10) $NR^fCO_2R^f$,

(11) $NR^fCON(R^f)_2$,

(12) $NR^fSO_2R^f$, provided that

R^f is not H,

(13) COR^f,

(14) CO_2R^f,

(15) $CON(R^f)_2$,

(16) $SO_2N(R^f)_2$,

(17) $OCON(R^f)_2$, or

(18) C_{3-8} cycloalkyl,

wherein said cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 3 groups of halo or C_{1-6} alkyl;

R^d is (1) a group selected from R^c,

(2) C_{1-10} alkyl,

(3) C_{2-10} alkenyl,

(3) C_{2-10} alkenyl,

(4) C_{2-10} alkynyl,

(5) aryl C_{1-10} alkyl, or

(6) heteroaryl C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from R^e;

R^e is (1) halogen,

(2) amino,

(3) carboxyl,

(4) C_{1-4} alkyl,

(5) C_{1-4} alkoxy,

(6) hydroxy,

(7) aryl,

(8) aryl C_{1-4} alkyl, or

(9) aryloxy;

R^f is (1) hydrogen,

(2) C_{1-10} alkyl,

(3) C_{2-10} alkenyl,

(4) C_{2-10} alkynyl,

(5) aryl,

(6) heteroaryl,

(7) aryl C_{1-15} alkyl,

(8) heteroaryl C_{1-15} alkyl,

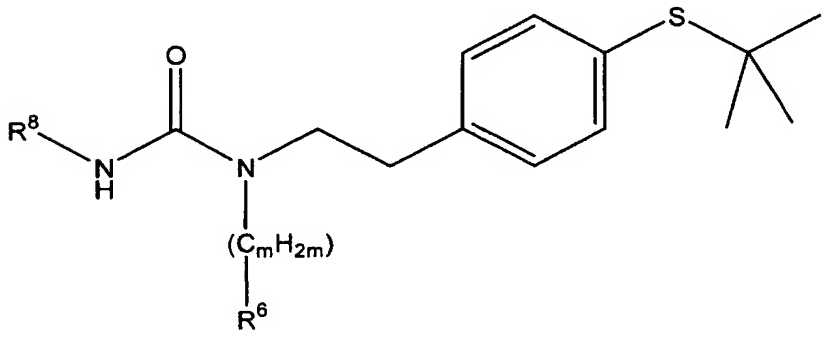
(9) C_{1-15} alkanoyl,

(10) C_{3-8} cycloalkyl;

wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkanoyl and cycloalkyl are optionally substituted with one to four groups selected from R^e;

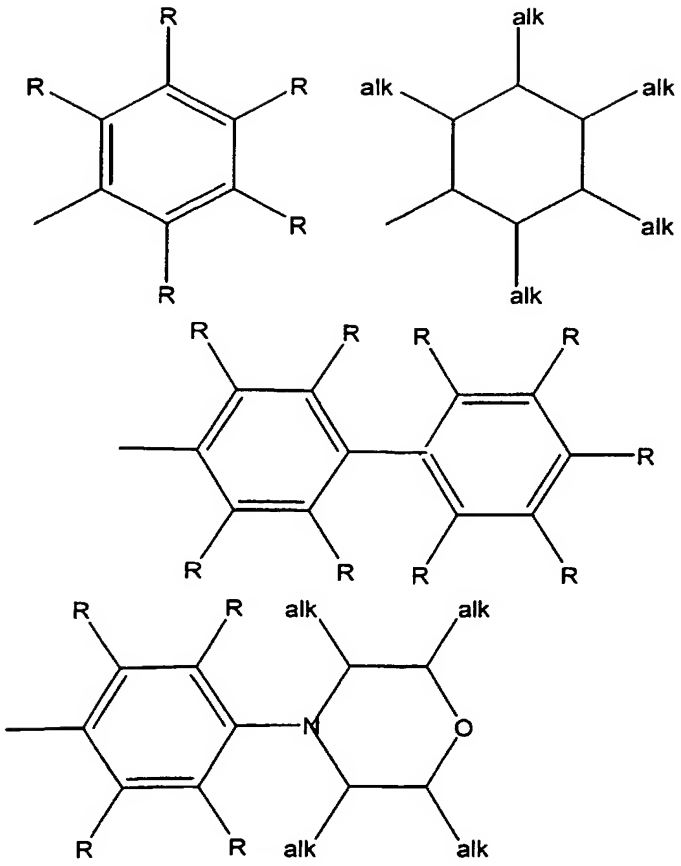
or a pharmaceutically acceptable salt thereof.

[00040] U.S. Patent No. 6,306,854 describes compounds that can serve as the PPARα agonists of the present invention. The compounds have the general structure of formula XI, or a salt thereof, where the general structure is:

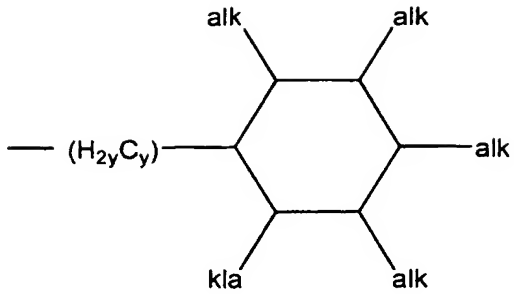


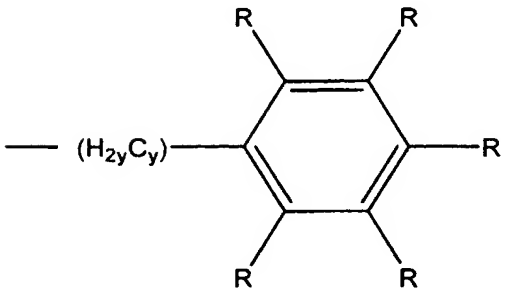
XI

wherein m is from 0 to 20, R^6 is selected from the group consisting of hydrogen and



and R^8 is selected from the group consisting of





where y is 0, 1, or 2, each alk is independently hydrogen or alkyl group containing 1 to 6 carbon atoms, each R group is independently hydrogen, halogen, cyano, --NO_2, phenyl, straight or branched alkyl or fluoroalkyl containing 1 to 6 carbon atoms and which can contain hetero atoms such as nitrogen, oxygen, or sulfur and which can contain functional groups such as ketone or ester, cycloalkyl containing 3 to 7 carbon atoms, or two R groups bonded to adjacent carbon atoms can, together with the carbon atoms to which they are bonded, form an aliphatic or aromatic ring or multi ring system, and where each depicted ring has no more that 3 alk groups.

[00041] Examples of preferred compounds that have the structure of formula II include:

2-(4-(2-(1-(4-biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid,

2-(4-(2-(1-(2-(4-morpholinophenyl)ethyl-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid;

2-(4-(2-(1-(cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid;

2-(4-(2-(1-heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenylthio)-2-methylpropionic acid;

2-(4-(2-(1-(2-chloro-4-(2-trifluoromethylphenyl)phenylmethyl)-3-(cyclohexyl)ureido)ethyl)phenylthio)-2-methylpropionic acid,

or a salt thereof.

[00042] Antagonists of PPARα inhibitors can also act as a PPARα agonist of the present invention. One such PPARα inhibitor, described as MK886, is discussed by Kehrer, J. P. *et al., Biochem. J., 356(Pt.3)*:899 - 906 (2001). Accordingly, any compound that interacted with MK886, or any other PPARα inhibitor, in a manner that interfered with or reduced its PPARα inhibitory activity, could be a PPARα agonist in the sense of this invention.

[00043] PPARα agonists that are useful in the present invention can be supplied by any source as long as the PPARα agonist is pharmaceutically acceptable. The PPARα agonists can be isolated and purified from natural sources or it can be synthesized. PPARα agonists are preferably of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[00044] Another component of the combination of the present invention is a cycloxygenase-2 selective inhibitor. The terms "cyclooxygenase-2 selective inhibitor", or "Cox-2 selective inhibitor", which can be used interchangeably herein, embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also include pharmaceutically acceptable salts of those compounds.

[00045] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1, divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than

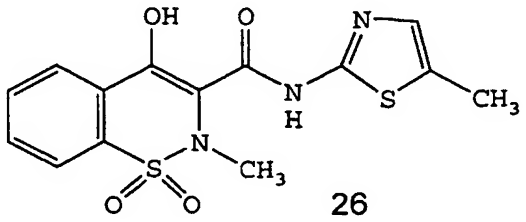
1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

[00046] As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred cyclooxygenase-2 selective inhibitors of the present invention have a cyclooxygenase-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[00047] Preferred cycloxoygenase-2 selective inhibitors have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

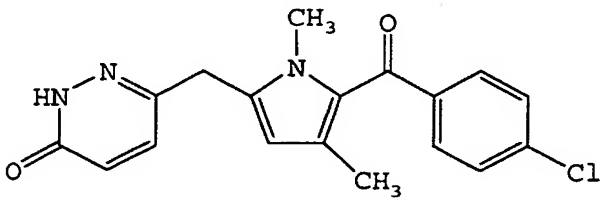
[00048] Also included within the scope of the present invention are compounds that act as prodrugs of cyclooxygenase-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is parecoxib sodium. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

[00049] The cyclooxygenase-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-

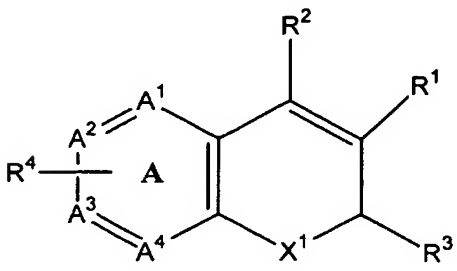
[00050] In another embodiment of the invention the cyclooxygenase-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[00051] In a another embodiment of the invention the cyclooxygenase-2 selective inhibitor is of the chromene/chroman structural class that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the compounds having a structure shown by general Formulas I, II, III, IV, V, and VI, shown below, and possessing, by way of example and not limitation, the structures disclosed in Table 3, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00052] Benzopyrans that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent No. 6,271,253. One such class of compounds is defined by the general formula shown below in formulas I:



I

27

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 -C_3 -alkyl, (optionally substituted phenyl)-C_1 -C_3 -alkyl, acyl and carboxy-C_1 –C_6 -alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 -C_3 -alkyl, phenyl-C_1 -C_3 -alkyl, C_1 -C_3 -perfluoroalkyl, chloro, C_1 –C_6 -alkylthio, C_1 –C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 –C_6 -alkylsulfonylaminocarbonyl and C_1 –C_6 -alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 –C_6 -alkyl and C_2 –C_6 -alkenyl;

wherein R^3 is selected from C_1 -C_3 -perfluoroalkyl, chloro, C_1 –C_6 -alkylthio, C_1 –C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl;

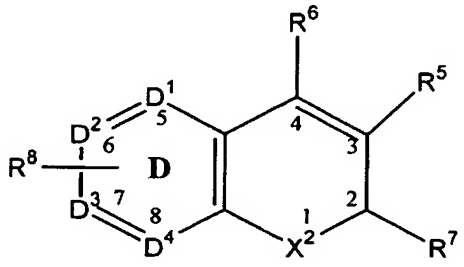
wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 -alkyl, C_2 –C_6 -alkenyl, C_2 –C_6 -alkynyl, halo-C_2 –C_6 -alkynyl, aryl-C_1 -C_3 -alkyl, aryl-C_2 –C_6 -alkynyl, aryl-C_2 –C_6 -alkenyl, C_1 –C_6 -alkoxy, methylenedioxy, C_1 –C_6 -alkylthio, C_1 –C_6 -alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 -alkoxy-C_1 –C_6 -alkyl, aryl-C_1 –C_6 -alkyloxy, heteroaryl-C_1 –C_6 -alkyloxy, aryl-C_1 –C_6 -alkoxy-C_1 –C_6 -alkyl, C_1 –C_6 -haloalkyl, C_1 –C_6 -haloalkoxy, C_1 –C_6 -haloalkylthio, C_1 –C_6 -haloalkylsulfinyl, C_1 –C_6 -haloalkylsulfonyl, C_1 -C_3 -(haloalkyl-$_1$ -C_3 -hydroxyalkyl, C_1 –C_6 -hydroxyalkyl, hydroxyimino-C_1 –C_6 -alkyl, C_1 –C_6 -alkylamino, arylamino, aryl-C_1 –C_6 -alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 -alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 -C_6 -alkylaminosulfonyl, heteroaryl-C_1 -C_6 -alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 -alkylsulfonyl, aryl-C_1 –C_6 -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 -alkylcarbonyl, heteroaryl-C_1 –C_6 -alkylcarbonyl, heteroarylcarbonyl,

arylcarbonyl, aminocarbonyl, C_1 –C_1 -alkoxycarbonyl, formyl, C_1 –C_6 -haloalkylcarbonyl and C_1 –C_6 -alkylcarbonyl; and

wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[00053] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes a compound having the structure of formula **II**:



II

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 -C_3 -alkyl, (optionally substituted phenyl)-C_1 -C_3 -alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1 -C_6 -alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 -C_3 -alkyl, phenyl-C_1 -C_3 -alkyl, C_1 -C_3 -perfluoroalkyl, chloro, C_1 -C_6 -alkylthio, C_1 -C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl; or wherein $CR^c R^b$ form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 -C_6 -alkylsulfonylaminocarbonyl and C_1 -C_6 -alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 -C_6 -alkynyl and C_2 -C_6 -alkenyl;

wherein R^7 is selected from C_1 -C_3 -perfluoroalkyl, chloro, C_1 -C_6 -alkylthio, C_1 -C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl;

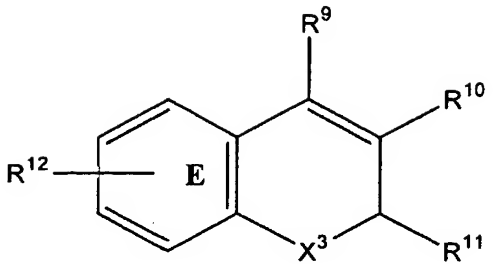
wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl, C_2 -C_6 -alkynyl, halo-C_2 -C_6 -alkynyl, aryl-C_1 -C_3 -alkyl, aryl-C_2 -C_6 -alkynyl, aryl-C_2 -C_6 -alkenyl, C_1 -C_6 -alkoxy, methylenedioxy, C_1 -C_6 -alkylthio, C_1 -C_6 -alkylsulfinyl, —$O(CF_2)_2$ O—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 -C_6 -alkoxy-C_1 -C_6 -alkyl, aryl-C_1 -C_6 -alkyloxy, heteroaryl-C_1 -C_6 -alkyloxy, aryl-C_1 -C_6 -alkoxy-C_1 -C_6 -alkyl, C_1 -C_6 -haloalkyl, C_1 -C_6 -haloalkoxy, C_1 -C_6 -haloalkylthio, C_1 -C_6 -haloalkylsulfinyl, C_1 -C_6 -haloalkylsulfonyl, C_1 -C_3 -(haloalkyl-C_1 -C_3 – hydroxyalkyl), C_1 -C_6 -hydroxyalkyl, hydroxyimino-C_1 -C_6 -alkyl, C_1 -C_6 -alkylamino, arylamino, aryl-C_1 -C_6 -alkylamino, heteroarylamino, heteroaryl-C_1 -C_6 -alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 -C_6 -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 -C_6 -alkylaminosulfonyl, heteroaryl-C_1 -C_6 -alkylaminosulfonyl, heterocyclylsulfonyl, C_1 -C_6 -alkylsulfonyl, aryl-C_1 -C_6 -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 -C_6 -alkylcarbonyl, heteroaryl-C_1 -C_6 -alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 -C_6 -alkoxycarbonyl, formyl, C_1 -C_6 -haloalkylcarbonyl and C_1 -C_6 -alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or

wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[00054] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula **III**:

[00055] Formula III is:



III

wherein X^3 is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^9 is selected from the group consisting of H and aryl;

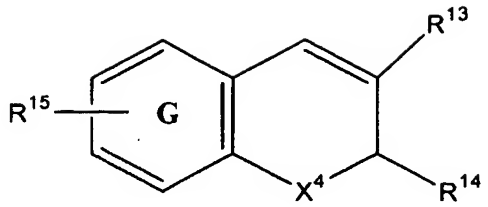
wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00056] A related class of compounds useful as cyclooxygenase-2 selective inhibitors in the present invention is described by Formulas **IV** and **V**:



IV

wherein X^4 is selected from O or S or NR^a ;

wherein R^a is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

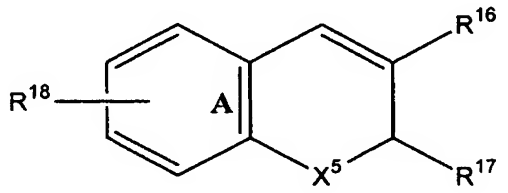
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00057] Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00058] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered

nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00059] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00060] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-

dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or

wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00061] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

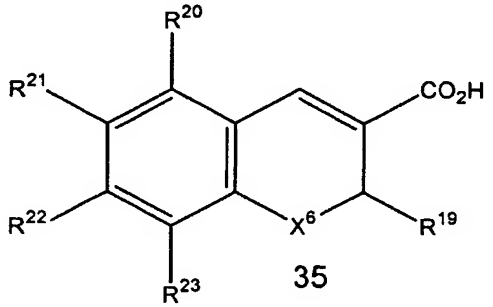
R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

[00062] The cyclooxygenase-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**:



VI

wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

[00063] The cyclooxygenase-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

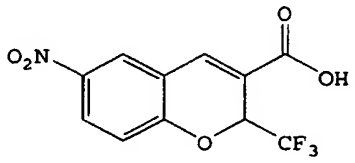
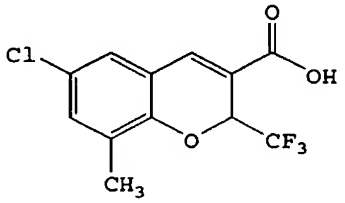
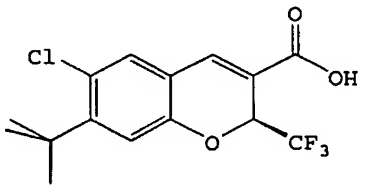
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

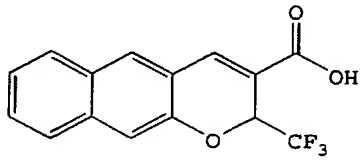
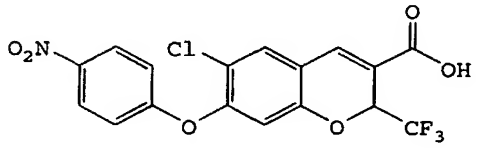
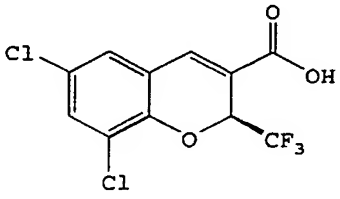
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

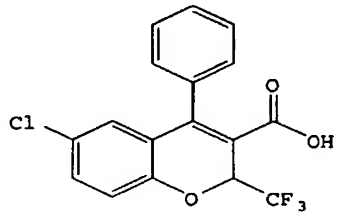
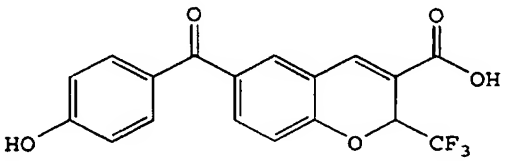
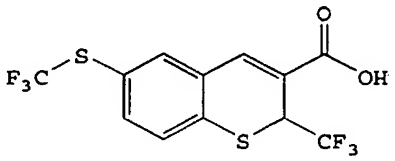
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

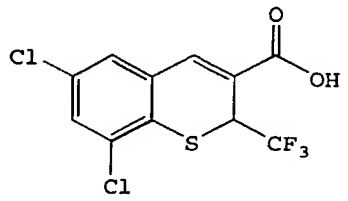
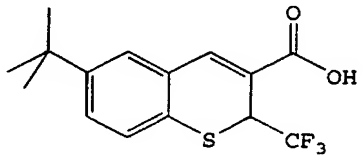
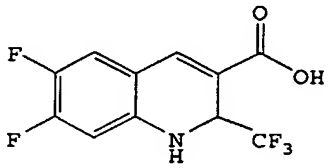
or an isomer or prodrug thereof.

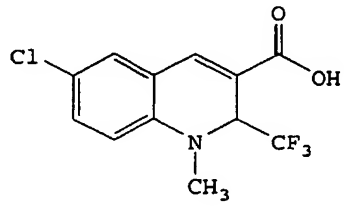
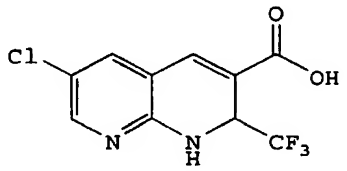
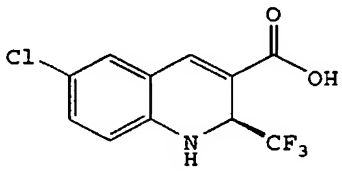
Table 3. Examples of Chromene Cox-2 Selective Inhibitors

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

[00064] Examples of specific compounds that are useful for the cyclooxygenase-2 selective inhibitor include (without limitation):

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

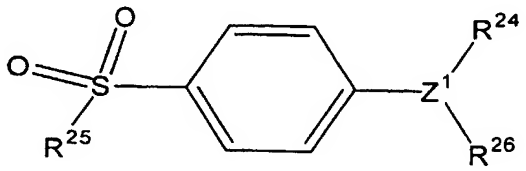
s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

[00065] In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-

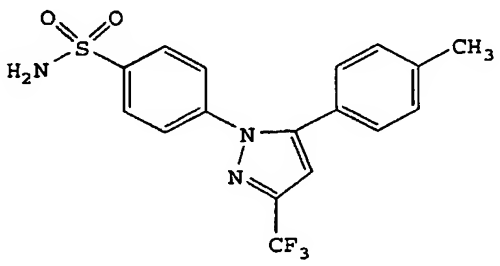
N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

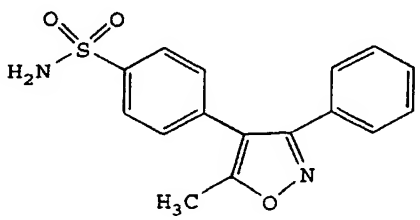
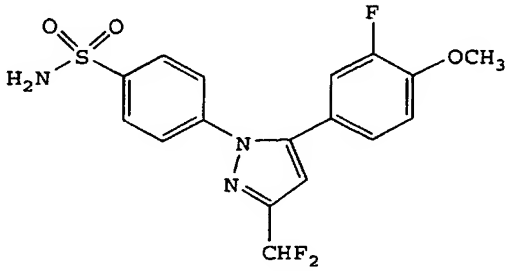
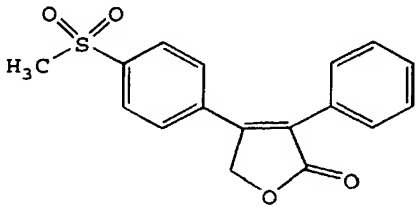
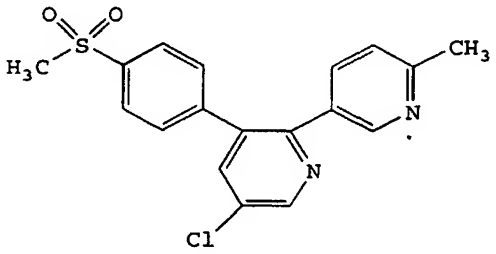
or a prodrug thereof.

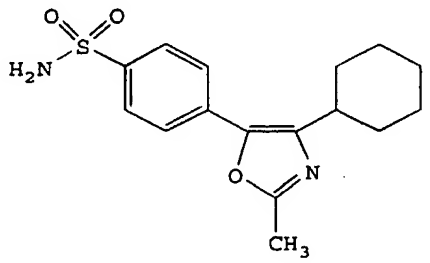
[00066] In a preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 4, which includes celecoxib (B-18), valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), or a prodrug thereof.

[00067] Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

Table 4. Examples of Tricyclic COX-2 Selective Inhibitors

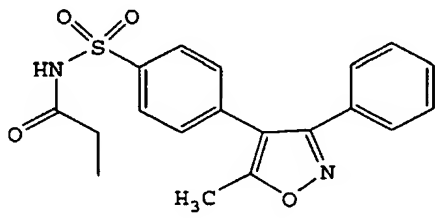
Compound Number	**Structural Formula**
B-18	

Compound Number	Structural Formula
B-19	
B-20	
B-21	
B-22	

Compound Number	Structural Formula
B-23	

[00068] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

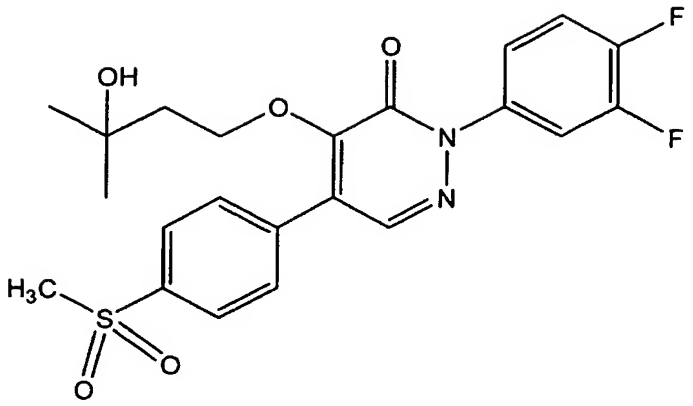
[00069] In a preferred embodiment of the invention, parecoxib (See, *e.g.* U.S. Patent No. 5,932,598), having the structure shown in B-24, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, (See, *e.g.*, U.S. Patent No. 5,633,272), may be advantageously employed as a source of a cyclooxygenase inhibitor.



B-24

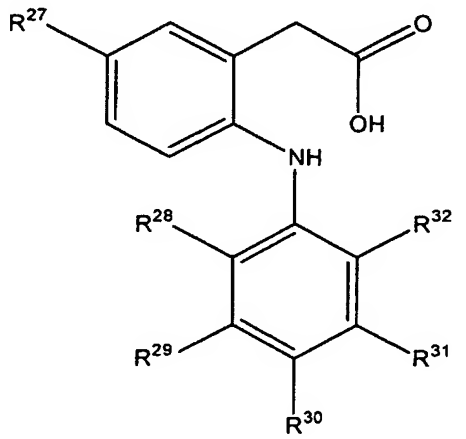
[00070] A preferred form of parecoxib is sodium parecoxib.

[00071] In another embodiment of the invention, the compound ABT-963 having the formula B-25 that has been previously described in International Publication number WO 00/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



B-25

[00072] In a further embodiment of the invention, the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula **VIII**:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[00073] A phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in Formula VIII,

wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

[00074] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor is a compound that has the structure shown in Formula VIII,

wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[00075] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib), having CAS Reg. No. 220991-20-8, and having the structure shown in Formula VIII,

wherein:

R^{27} is methyl;

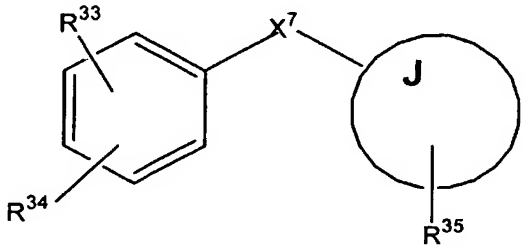
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

[00076] Compounds that have a structure similar to that shown in Formula VIII, which can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,310,099, 6,291,523, and 5,958,978.

[00077] Other cyclooxygenase-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X is O; J is 1-phenyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 4-NO_2; and there is no R^{35} group, (nimesulide), and

X is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$NHSO_2CH_3$, (flosulide); and

X is O; J is cyclohexyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 5-NO_2; and there is no R^{35} group, (NS-398); and

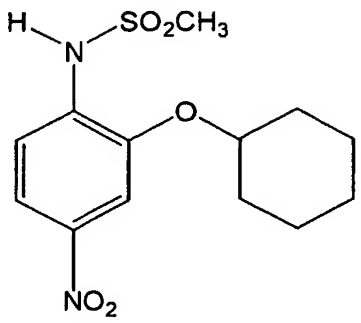
X is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); and

X is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-$NHSO_2CH_3$, (RWJ-63556); and

X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

[00078] Further information on the applications of the Cox-2 selective inhibitor N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res., 90(4)*:406 - 412 (1999); Falgueyret, J.-P. *et al.*, in *Science Spectra,* available at: http://www.gbhap.com/Science_Spectra/20-1-article.htm

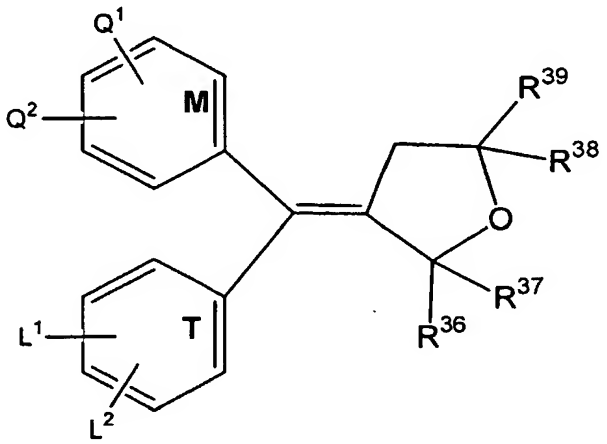
(06/06/2001); and Iwata, K. *et al.*, in *Jpn. J. Pharmacol., 75(2):*191 - 194 (1997).



B-26

[00079] An evaluation of the anti-inflammatory activity of the cyclooxygenase-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[00080] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are:

a phenyl radical,

a naphthyl radical,

a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or

a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is:

an —$S(O)_n$ —R group, in which n is an integer equal to 0, 1 or 2 and R is:

a lower alkyl radical having 1 to 6 carbon atoms or

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an -SO_2NH_2 group;

and is located in the para position,

the others independently being:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a trifluoromethyl radical, or

a lower O-alkyl radical having 1 to 6 carbon atoms, or

Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom, or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

[00081] Particular materials that are included in this family of compounds, and which can serve as the cyclooxygenase-2 selective inhibitor in the present invention, include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

[00082] Cyclooxygenase-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

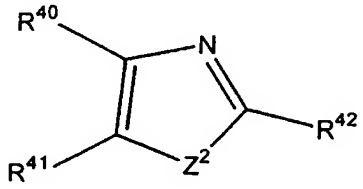
[00083] Information about S-33516, mentioned above, can be found in *Current Drugs Headline News*, at http://www.current-drugs.com/NEWS/Inflam1.htm, 10/04/2001, where it was reported that S-33516 is a tetrahydroisoinde derivative which has IC_{50} values of 0.1 and 0.001 mM against cyclooxygenase-1 and cyclooxygenase-2, respectively. In human whole blood, S-33516 was reported to have an ED_{50} = 0.39 mg/kg.

[00084] Compounds that may act as cyclooxygenase-2 selective inhibitors include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[00085] Compounds that may act as cyclooxygenase-2 inhibitors include conjugated linoleic acid that is described in U.S. Patent No. 6,077,868.

[00086] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209.

Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

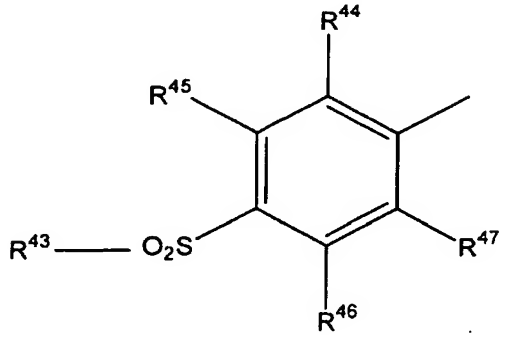


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



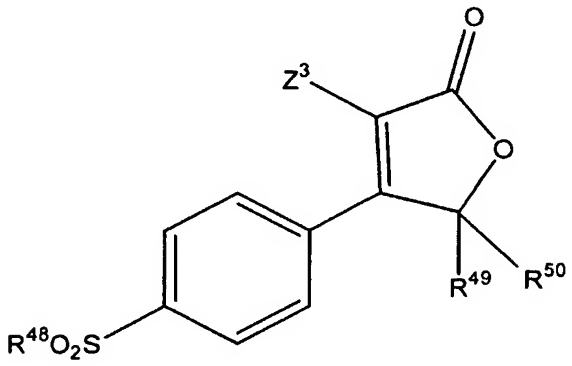
wherein:

R^{43} is lower alkyl, amino or lower alkylamino; and

R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy or amino, provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl, and a pharmaceutically acceptable salt thereof.

[00087] Cox-2 selective inhibitors that are useful in the subject method and compositions can include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

Z^3 is selected from the group consisting of:

(a) linear or branched C_{1-6} alkyl,

(b) linear or branched C_{1-6} alkoxy,

(c) unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_{1-3} alkoxy,

(4) CN,

(5) C_{1-3} fluoroalkyl

(6) C_{1-3} alkyl,

(7) $-CO_2H$;

R^{48} is selected from the group consisting of NH_2 and CH_3,

R^{49} is selected from the group consisting of:

C_{1-6} alkyl unsubstituted or substituted with C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl;

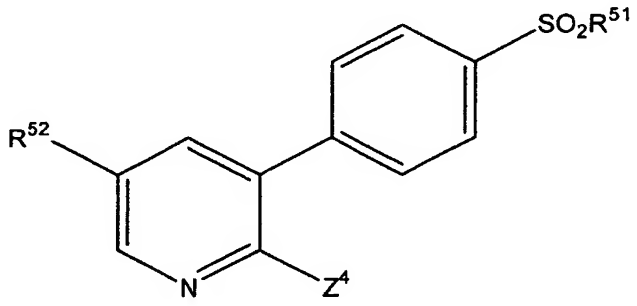
R^{50} is selected from the group consisting of:

C_{1-6} alkyl unsubstituted or substituted with one, two or three fluoro atoms; and

C_{3-6} cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

[00088] Materials that can serve as cyclooxygenase-2 selective inhibitors include pyridines that are described in U.S. Patent Nos. 6, 369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and which have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$,

(d) $NHCH_3$;

Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof),

wherein the substituents are chosen from the group consisting of:

(a) hydrogen,

(b) halo,

(c) C_{1-6} alkoxy,

(d) C_{1-6} alkylthio,

(e) CN,

(f) C_{1-6} alkyl,

(g) C_{1-6} fluoroalkyl,

(h) N_3,

(i) $-CO_2R^{53}$,

(j) hydroxy,

(k) $-C(R^{54})(R^{55})—OH$,

(l) $-C_{1-6}$alkyl-$CO_2—R^{56}$,

(m) C_{1-6}fluoroalkoxy;

R^{52} is chosen from the group consisting of:

(a) halo,

(b) C_{1-6}alkoxy,

(c) C_{1-6} alkylthio,

(d) CN,

(e) C_{1-6} alkyl,

(f) C_{1-6} fluoroalkyl,

(g) N_3,

(h) $—CO_2R^{57}$,

(i) hydroxy,

(j) $—C(R^{58})(R^{59})—OH$,

(k) $—C_{1-6}$alkyl-$CO_2—R^{60}$,

(l) C_{1-6}fluoroalkoxy,

(m) NO_2,

(n) $NR^{61}R^{62}$, and

(o) $NHCOR^{63}$;

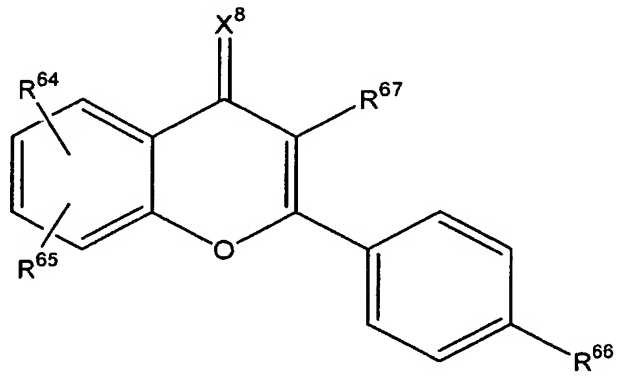
R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, are each independently chosen from the group consisting of:

(a) hydrogen, and

(b) C_{1-6}alkyl;

or R^{54} and R^{55}, R^{58} and R^{59} or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[00089] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

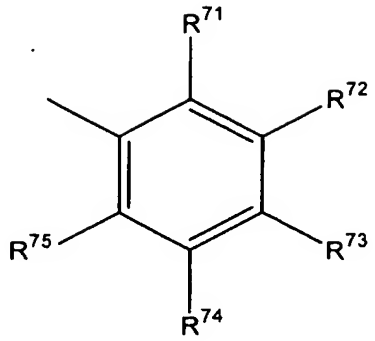
wherein:

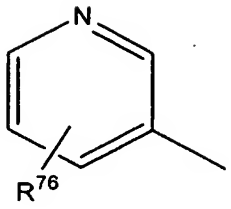
X^8 is an oxygen atom or a sulfur atom;

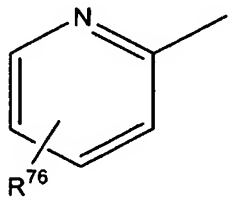
R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

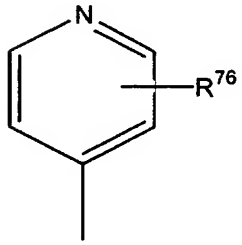
R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0~2, R^{68} is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula: NR^{69} R^{70} wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1 -C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1 -C_6 lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:









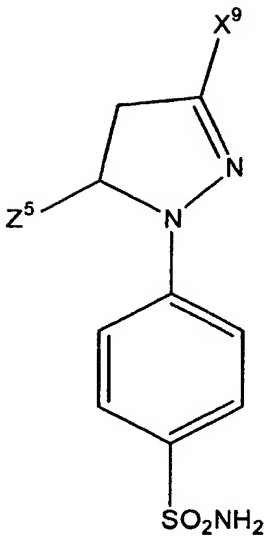
wherein:

R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: NR^{69} R^{70}, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

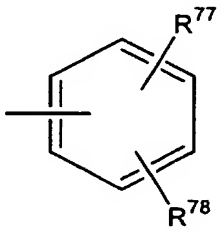
[00090] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

X^9 is selected from the group consisting of C_1 -C_6 trihalomethyl, preferably trifluoromethyl; C_1 -C_6 alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



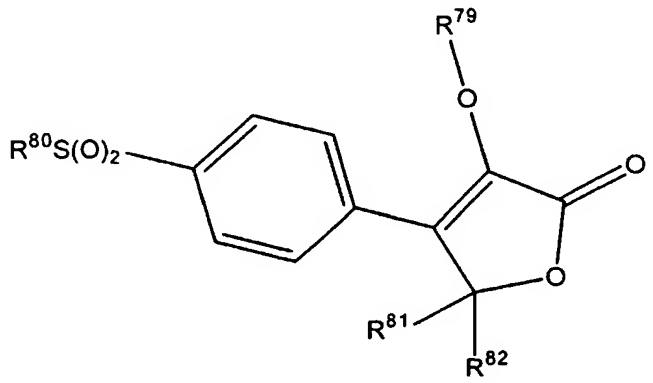
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1 -C_6 alkyl, preferably C_1 -C_3 alkyl; C_1 -C_6 alkoxy, preferably C_1 -C_3 alkoxy; carboxy; C_1 -C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[00091] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

R^{79} is a mono-, di-, or tri-substituted C_{1-12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_{3-12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_{5-12} cycloalkynyl, wherein the substituents are chosen from the group consisting of:

(a) halo, selected from F, Cl, Br, and I,

(b) OH,

(c) CF_3,

(d) C_{3-6} cycloalkyl,

(e) =O,

(f) dioxolane,

(g) CN; and

R^{80} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$,

(d) $NHCH_3$;

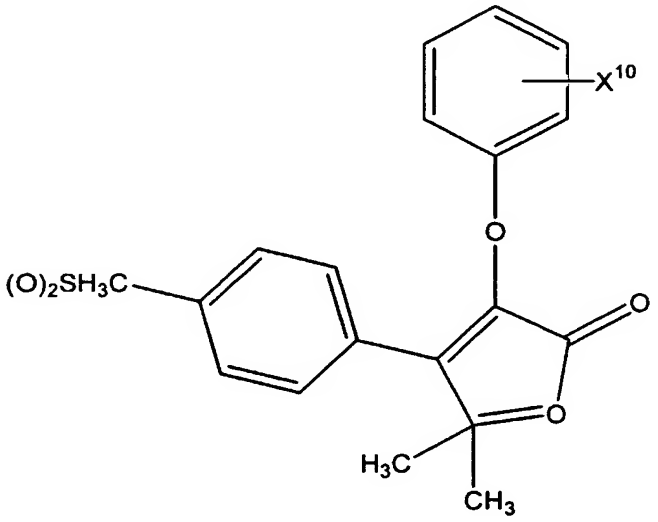
R^{81} and R^{82} are independently chosen from the group consisting of:

(a) hydrogen,

(b) C_{1-10} alkyl;

or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

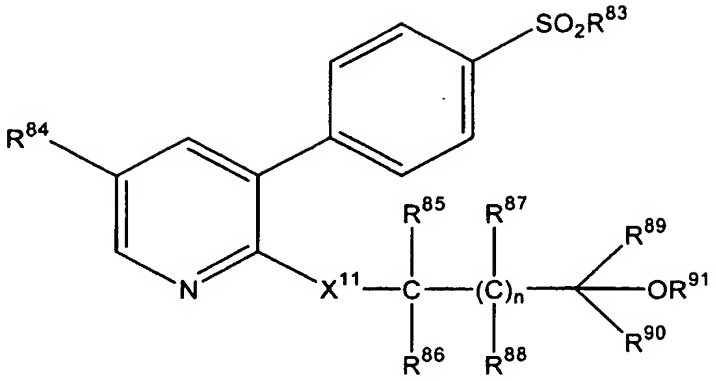
[00092] Formula **XVIII** is:



XVIII

X^{10} is fluoro or chloro.

[00093] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

or a pharmaceutically acceptable salt thereof,

wherein:

X^{11} is selected from the group consisting of:

(a) O,

(b) S,

(c) bond;

n is 0 or 1;

R^{83} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$;

R^{84} is chosen from the group consisting of:

(a) halo,

(b) C_{1-6} alkoxy,

(c) C_{1-6} alkylthio,

(d) CN,

(e) C_{1-6} alkyl,

(f) C_{1-6} fluoroalkyl,

(g) N_3,

(h) $—CO_2 R^{92}$,

(i) hydroxy,

(j) $—C(R^{93})(R^{94})—OH$,

(k) $—C_{1-6}$ alkyl-$CO_2 —R^{95}$,

(l) C_{1-6} fluoroalkoxy,

(m) NO_2,

(n) $NR^{96}R^{97}$,

(o) $NHCOR^{98}$;

R^{85} to R^{98} are independantly chosen from the group consisting of

(a) hydrogen,

(b) C_{1-6} alkyl;

or R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

[00094] One preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is a bond.

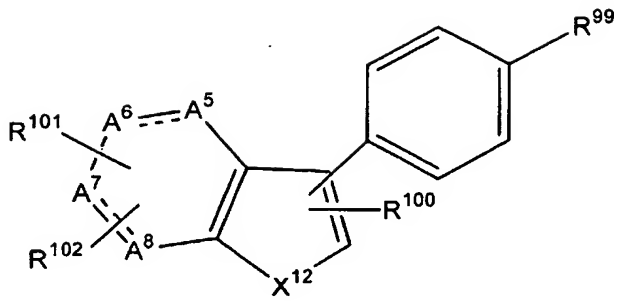
[00095] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is O.

[00096] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is S.

[00097] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{83} is CH_3.

[00098] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{84} is halo or C_{1-6} fluoroalkyl.

[00099] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:

$—A^5=A^6—A^7=A^8—$ is selected from the group consisting of:

(a) —CH=CH—CH=CH—,

(b) $—CH_2—CH_2—CH_2—C(O)—$, $—CH_2—CH_2—C(O)—CH_2—$, $—CH_2—C(O)—CH_2—CH_2$, $—C(O)—CH_2—CH_2—CH_2$,

(c) $—CH_2—CH_2—C(O)—$, $—CH_2—C(O)—CH_2—$, $—C(O)—CH_2—CH_2—$

(d) $—CH_2—CH_2—O—C(O)—$, $CH_2—O—C(O)—CH_2—$, $—O—C(O)—CH_2—CH_2—$,

(e) $—CH_2—CH_2—C(O)—O—$, $—CH_2—C(O)—OCH_2—$, $—C(O)—O—CH_2—CH_2—$,

(f) $—C(R^{105})_2—O—C(O)—$, $—C(O)—O—C(R^{105})_2—$, $—O—C(O)—C(R^{105})_2—$, $—C(R^{105})_2—C(O)—O—$,

(g) —N=CH—CH=CH—,

(h) —CH=N—CH=CH—,

(i) —CH=CH—N=CH—,

(j) —CH=CH—CH=N—,

(k) —N=CH—CH=N—,

(l) —N=CH—N=CH—,

(m) —CH=N—CH=N—,

(n) —S—CH=N—,

(o) —S—N=CH—,

(p) —N=N—NH—,

(q) —CH=N—S—, and

(r) —N=CH—S—;

R^{99} is selected from the group consisting of:

(a) $S(O)_2 CH_3$,

(b) $S(O)_2 NH_2$,

(c) $S(O)_2 NHCOCF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHCOCF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of:

(a) C_{1-6} alkyl,

(b) C_{3-7}, cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

(3) C_{1-6} alkoxy,

(4) C_{1-6} alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6} alkyl,

(8) N_3,

(9) $—CO_2 H$,

(10) $—CO_2 —C_{1-4}$ alkyl,

(11) $—C(R^{103})(R^{104})—OH$,

(12) $—C(R^{103})(R^{104})—O—C_{1-4}$ alkyl, and

(13) $—C_{1-6}$ alkyl-$CO_2 —R^{106}$;

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero

atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkoxy,

(5) C_{1-6} alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{103})(R^{104})$—OH, and

(10) —$C(R^{103})(R^{104})$—O—C_{1-4} alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of –A^5=A^6—A^7=A^8— and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) —Q^3 wherein Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})$OH,

(f) —O—Q^4,

(g) —S—Q^4, and

(h) optionally substituted:

(1) —C_{1-5} alkyl-Q^3,

(2) —O—C_{1-5} alkyl-Q^3,

(3) —S—C_{1-5} alkyl-Q^3,

(4) —C_{1-3} alkyl-O—C_{1-3} alkyl-Q^3,

(5) —C_{1-3} alkyl-S—C_{1-3} alkyl-Q^3,

(6) —C_{1-5} alkyl-O—Q^4,

(7) —C_{1-5} alkyl-S—Q^4,

wherein the substituent resides on the alkyl chain and the substituent is C_{1-3} alkyl, and Q^3 is Q^4, CO_2H, $C(R^{103})(R^{104})OH$ Q^4 is CO_2—C_{1-4} alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})O$—C_{1-4} alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-6} alkyl; or

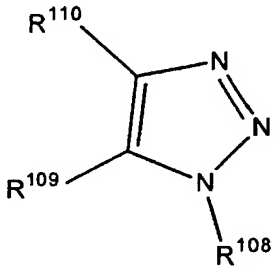
R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_{1-6} alkyl;

R^{107} is hydrogen, C_{1-6} alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, —$C(R^{107})$=$C(R^{107})$—; —$C(R^{107})$=N—; —N=$C(R^{107})$—.

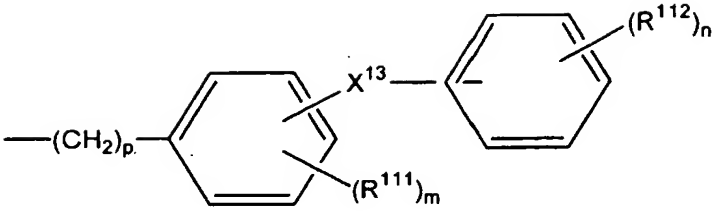
[000100] Compounds that may act as cyclooxygenase-2 inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

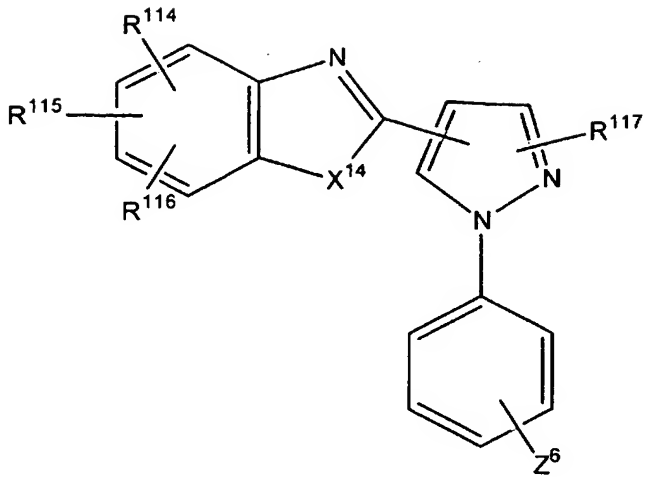
R^{108} is:



wherein:

[000101] p is 0 to 2; m is 0 to 4; and n is 0 to 5; X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or $C=NR^{113}$ where R^{113} is hydrogen, loweralkyl, hydroxy, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano; and, R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifuloromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, formamido or guanidino; and R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

[000102] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyrazole derivatives that are described in U.S. Patent 6,136,831. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen, R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or lower alkanoyloxy;

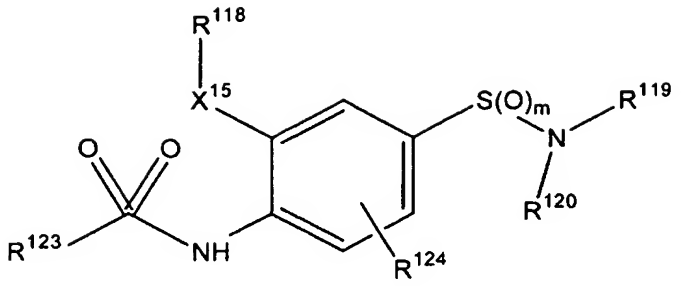
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

[000103] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ $-X^{16}$; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$—X^{16};

X^{16} denotes halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121};

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C- atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

R^{124} denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which

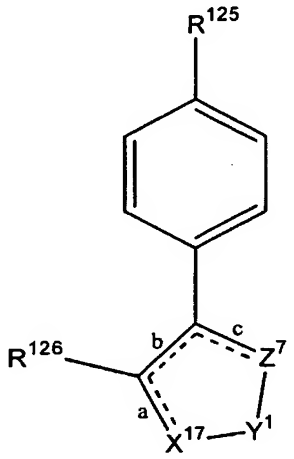
can optionally be mono- or polysubstituted by halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2R^{121}, —OCO_2R^{121}, —CN, —$CONR^{121}OR^{122}$, —$CONR^{121}R^{122}$, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2R^{121}$, —$NR^{121}R^{122}$, —$NHC(O)R^{121}$, —$NHS(O)_2R^{121}$, or a polyfluoroalkyl group;

R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

[000104] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones that are described in U.S. Patent 6,239,173. Such 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones have the formula shown below in formula **XXIV**:



XXIV

or pharmaceutically acceptable salts thereof wherein:

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) —$CH_2CH_2CH_2$—,

(b) —$C(O)CH_2CH_2$—,

(c) —$CH_2CH_2C(O)$—,

(d) —$CR^{129}(R^{129'})$—O—C(O)—,

(e) —C(O)—O—$CR^{129}(R^{129'})$—,

(f) —CH_2 —NR^{127} —CH_2 —,

(g) —CR^{129} ($R^{129'}$)—NR^{127} —C(O)—,

(h) —CR^{128}=$CR^{128'}$ —S—,

(i) —S—CR^{128}=$CR^{128'}$ —,

(j) —S—N=CH—,

(k) —CH=N—S—,

(l) —N=CR^{128} —O—,

(m) —O—CR4=N— ,

(n) —N=CR^{128} —NH—,

(o) —N=CR^{128} —S—, and

(p) —S—CR^{128}=N—,

(q) —C(O)—NR^{127} —CR^{129} ($R^{129'}$)—,

(r) —R^{127} N—CH=CH— provided R_{122} is not —$S(O)_2CH_3$,

(s) —CH=CH—NR^{127} — provided R^{125} is not —$S(O)_2CH_3$,

when side b is a double bond, and sides a and c are single bonds; and

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) =CH—O—CH=, and

(b) =CH—NR^{127} —CH=,

(c) =N—S—CH=,

(d) =CH—S—N=,

(e) =N—O—CH=,

(f) =CH—O—N=,

(g) =N—S—N=,

(h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

(a) $S(O)_2$ CH_3,

(b) $S(O)_2$ NH_2,

(c) $S(O)_2$ $NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_{1-6} alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl,

wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_{1-6} alkoxy,

(4) C_{1-6} alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6} alkyl,

(8) N_3,

(9) $—CO_2H$,

(10) $—CO_2—C_{1-4}$ alkyl,

(11) $—C(R^{129})(R^{130})—OH$,

(12) $—C(R^{129})(R^{130})—O—C_{1-4}$ alkyl, and

(13) $—C_{1-6}$ alkyl-$CO_2—R^{129}$;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkoxy,

(5) C_{1-6} alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{129})(R^{130})$—OH, and

(10) —$C(R^{129})(R^{130})$—O—C_{1-4} alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) hydroxyC_{1-6} alkyl,

(f) —C(O)—C_{1-6} alkyl,

(g) optionally substituted:

(1) —C_{1-5} alkyl-Q^5,

(2) —C_{1-3} alkyl-O—C_{1-3} alkyl-Q^5,

(3) —C_{1-3} alkyl-S—C_{1-3} alkyl-Q^5,

(4) —C_{1-5} alkyl-O—Q^5, or

(5) —C_{1-5} alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl;

(h) –Q^5;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) –Q^5,

(f) —O—Q^5;

(g) —S—Q^5, and

(h) optionally substituted:

(1) —C_{1-5} alkyl-Q^5,

(2) —O—C_{1-5} alkyl-Q^5,

(3) —S—C_{1-5} alkyl-Q^5,

(4) —C_{1-3} alkyl-O—C_{1-3} alkyl-Q^5,

(5) —C_{1-3} alkyl-S—C_{1-3} alkyl-Q^5,

(6) —C_{1-5} alkyl-O—Q^5,

(7) —C_{1-5} alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of:

(a) hydrogen,

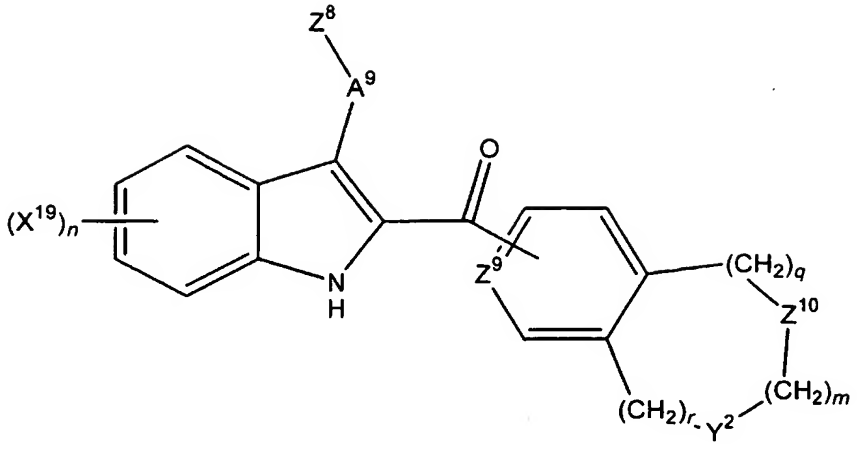
(b) C_{1-6} alkyl;

or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2H, CO_2 —C_{1-4} alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or $C(R^{131})(R^{132})(O—C_{1-4}$ alkyl);

provided that when X—Y—Z is —S—CR^{128}=$CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

[000105] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bicycliccarbonyl indole compounds that are described in U.S. Patent No. 6,303,628. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein

A^9 is C_{1-6} alkylene or —NR^{133} —;

Z^8 is $C(=L^3)R^{134}$, or SO_2 R^{135} ;

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from —CH_2 —, O, S and —N—R^{133} ;

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(C_{1-4} alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

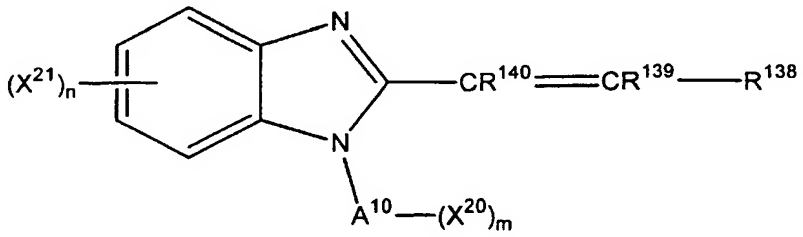
R^{133} is hydrogen or C_{1-4} alkyl;

R^{134} is hydroxy, C_{1-6} alkyl, halo-substituted C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-4} alkyl(C_{3-7} cycloalkoxy), —NR^{136} R^{137}, C_{1-4} alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy and nitro;

R^{135} is C_{1-6} alkyl or halo-substituted C_{1-6} alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, C_{1-6} alkyl and halo-substituted C_{1-6} alkyl.

[000106] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, halo-substituted C_1 -C_4 alkyl, hydroxy-substituted C_1 -C_4 alkyl, (C_1 -C_4 alkoxy)C_1 -C_4 alkyl, halo-substituted C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino, N, N-di(C_1 -C_4 alkyl)amino, [N-(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, [N, N-di(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, N-(C_1 -C_4 alkanoyl)amonio, N-(C_1 -C_4 alkyl)(C_1 -C_4 alkanoyl)amino, N-[(C_1 -C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 -C_4 alkyl)sulfonyl]amino, C_1 -C_4 alkanoyl, carboxy, (C_1 -C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1 -C_4 alkyl)amino]carbonyl, [N, N-di(C_1 -C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 -C_4 alkyl)thio, (C_1 -C_4 alkyl)sulfinyl, (C_1 -C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 -C_4

alkyl)amino]sulfonyl and [N, N-di(C_1 -C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, halo-substituted C_1 -C_4 alkyl, hydroxy-substituted C_1 -C_4 alkyl, (C_1 -C_4 alkoxy)C_1 -C_4 alkyl, halo-substituted C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino, N, N-di(C_1 -C_4 alkyl)amino, [N-(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, [N, N-di(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, N-(C_1 -C_4 alkanoyl)amino, N-(C_1 -C_4 alkyl)-N-(C_1 -C_4 alkanoyl) amino, N-[(C_1 -C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 -C_4 alkyl)sulfonyl]amino, C_1 -C_4 alkanoyl, carboxy, (C_1 -C_4 alkoxy)cabonyl, cabamoyl, [N-(C_1 -C_4 alkyl) amino]carbonyl, [N, N-di(C_1 -C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1 -C_4 alkyl)thio, (C_1 -C_4 alkyl)sulfinyl, (C_1 -C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 -C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 -C_4 alkyl)amino]sulfonyl;

R^{138} is selected from hydrogen,

straight or branched C_1 -C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

C_3 –C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are indepently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

C_4 –C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, halo-substituted C_1 -C_4 alkyl, hydroxy-substituted C_1 -C_4 alkyl, (C_1 -C_4 alkoxy)C_1 -C_4 alkyl, halo-substituted C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino, N, N-di(C_1 -C_4 alkyl)amino, [N-(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, [N, N-di(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, N-(C_1

-C_4 alkanoyl)amino, N-[C_1 -C_4 alkyl)(C_1 -C_4 alkanoyl)]amino, N-[(C_1 -C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1 -C_4 alkyl)sulfonyl]amino, C_1 -C_4 alkanoyl, carboxy, (C_1 -C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1 -C_4 alky)amino]carbonyl, [N, N-di(C_1 -C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 -C_4 alkyl)thio, (C_1 -C_4 alkyl)sulfinyl, (C_1 -C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 -C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 -C_4 alkyl)amino]sulfonyl; and

heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20} ;

R^{139} and R^{140} are independently selected from:

hydrogen,

halo,

C_1 -C_4 alkyl,

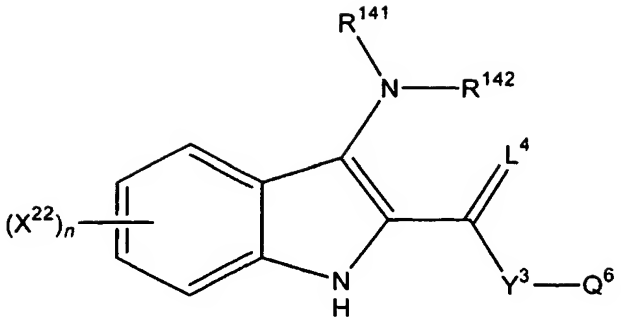
phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3 –C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

[000107] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

and the pharmaceutically acceptable salts thereof,

wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_{1-4} alkylidene;

Q^6 is:

(a) C_{1-6} alkyl or halosubstituted C_{1-6} alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkoxy, amino and mono- or di-(C_{1-4} alkyl)amino,

(b) C_{3-7} cycloalkyl optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_{1-4} alkyl, halosubstituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_{1-4}$ alkyl$)_2$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_{1-4} alkyl), C_{1-4} alkyl-OH, C_{1-4} alkyl-OR^{143}, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_{1-4} alkyl, CF_3, hydroxy, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic

group being substituted with up to three substitutents independently selected from:

(d-1) halo, C_{1-4} alkyl, halosubstituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, C_{1-4} alkyl-OH, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_{1-4}$ alkyl$)_2$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_{1-4} alkyl), C_{1-4} alkyl-OR^{143}, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, OCF_3, SR^{143}, $SO_2 CH_3$, $SO_2 NH_2$, amino, C_{1-4} alkylamino and $NHSO_2 R^{143}$;

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_{1-6} alkyl optionally substituted with a substituent selected independently from hydroxy, OR^{143}, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, $CO_2 H$, CO_2 (C_{1-4} alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl$)_2$;

R^{142} is:

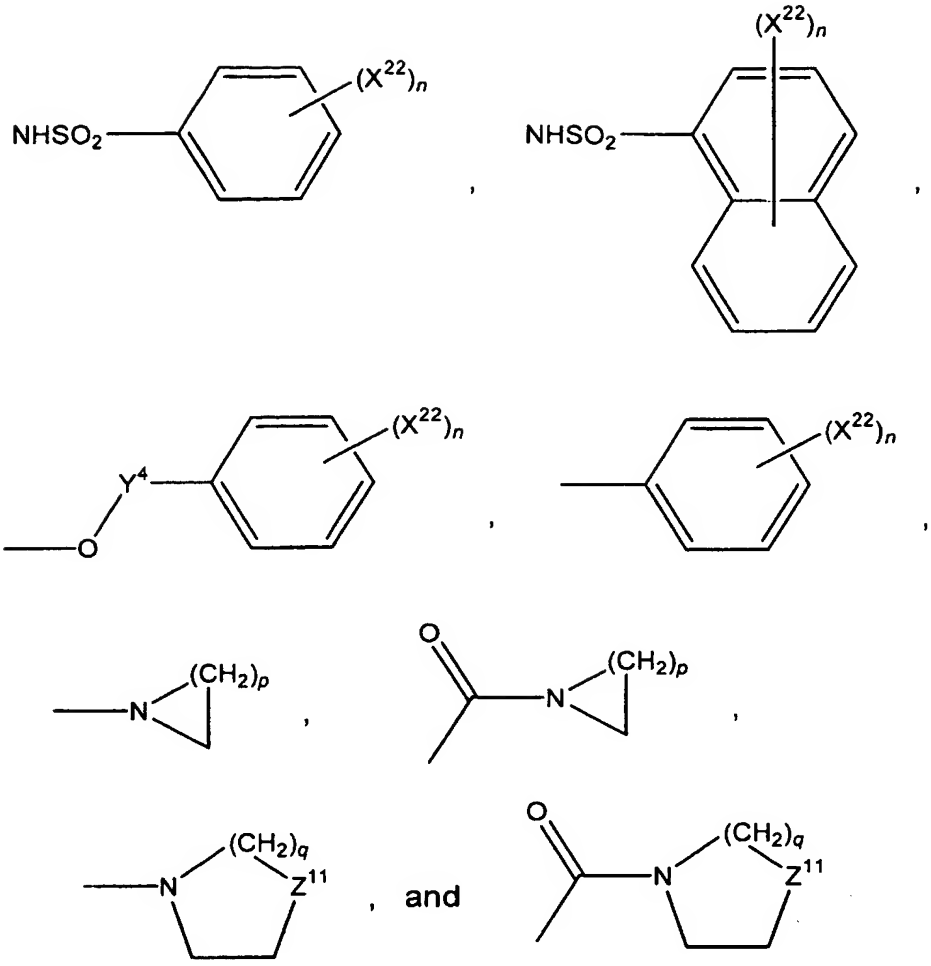
(a) hydrogen,

(b) C_{1-4} alkyl,

(c) $C(O)R^{145}$,

wherein R^{145} is selected from:

(c-1) C_{1-22} alkyl or C_{2-22} alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:
(c-1-1) halo, hydroxy, OR^{143}, $S(O)_m R^{143}$, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, $CO_2 H$, CO_2 (C_{1-4} alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulae:



(c-2) C_{1-22} alkyl or C_{2-22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) $-Y^5-C_{3-7}$ cycloalkyl or $-Y^5-C_{3-7}$ cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_{1-4} alkyl, hydroxy, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl)$_2$,

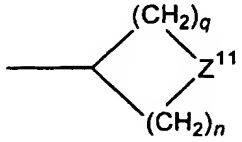
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_{1-8} alkyl, C_{1-4} alkyl-OH, hydroxy, C_{1-8} alkoxy, halosubstituted C_{1-8} alkyl, halosubstituted C_{1-8} alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_{1-4}$ alkyl), $SO_2 N(C_{1-4}$ alkyl)$_2$, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_{1-4} alkyl, hydroxy, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, CO_2 H, CO_2 (C_{1-4} alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_{1-8} alkyl, C_{1-4} alkyl-OH, hydroxy, C_{1-8} alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, CO_2 H and CO_2 (C_{1-4} alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, CO_2 H, CO_2 (C_{1-4} alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl)$_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstitutued C_{1-4} alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, nitro, halosubstitutued C_{1-4} alkyl, CN, CO_2 H, CO_2 (C_{1-4} alkyl), C_{1-4} alkyl-OH, C_{1-4} alkylOR^{143}, $CONH_2$, $CONH(C_{1-4}$ alkyl) or $CON(C_{1-4}$ alkyl)$_2$;

R^{143} is C_{1-4} alkyl or halosubstituted C_{1-4} alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_{1-6} alkyl, halosubstitutued C_{1-4} alkyl or $-Y^5$-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, CF_3, OCF_3, CN and nitro;

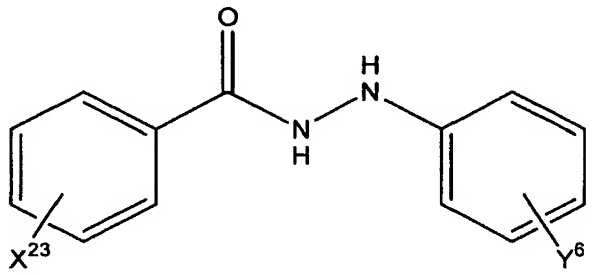
with the proviso that a group of formula $-Y^5$—Q is not methyl or ethyl when X^{22} is hydrogen;

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

[000108] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII**:

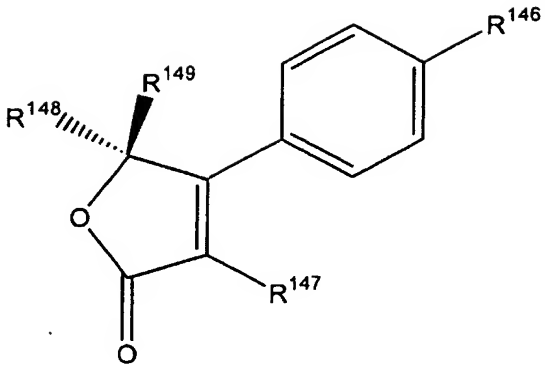


XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino or other oxygen and sulfur containing functional groups such as hydroxy, methoxy and methylsulfonyl.

[000109] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX**:



XXIX

or a pharmaceutical salt thereof,

wherein:

R^{146} is selected from the group consisting of SCH_3, $—S(O)_2 CH_3$ and $—S(O)_2 NH_2$;

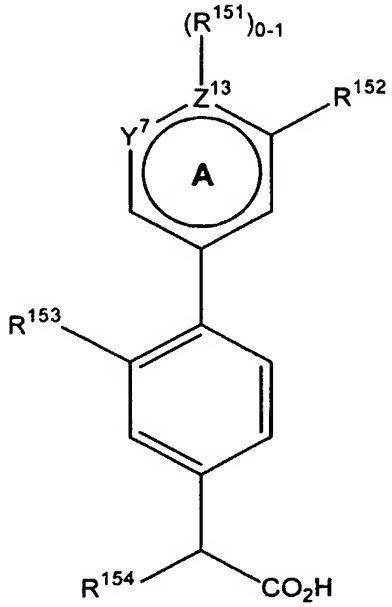
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_{1-4} alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_{1-4} alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[000110] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



XXX

or a pharmaceutically acceptable salt, ester or tautomer thereof,

wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an energetically stable configuration planar with ring A to within about 15 degrees;

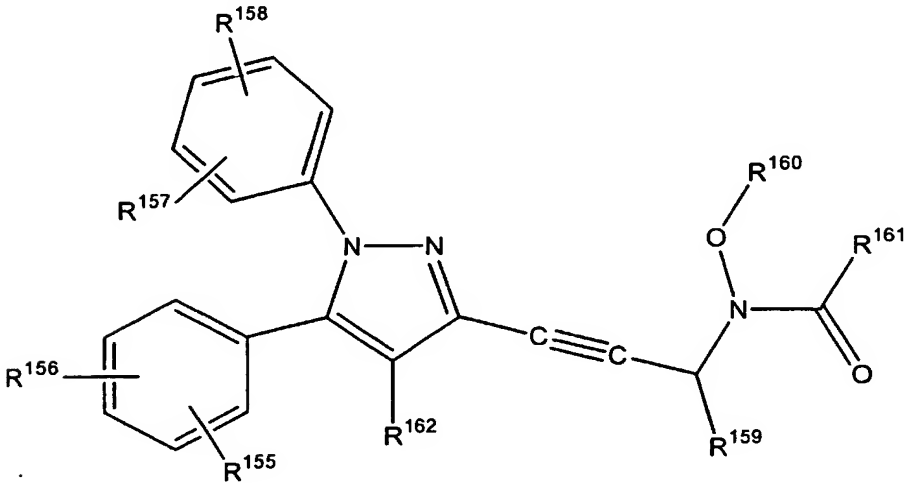
said ring D further being substituted with 1 R^a group selected from the group consisting of: C_{1-2} alkyl, —OC_{1-2} alkyl, —NHC_{1-2} alkyl, —$N(C_{1-2}$ alkyl$)_2$, —$C(O)C_{1-2}$ alkyl, —S—C_{1-2} alkyl and —$C(S)C_{1-2}$ alkyl;

Y^7 represents N, CH or C—OC_{1-3} alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

[000111] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:



XXXI

wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_{1-5} alkyl, C_{1-5} alkoxy, phenyl, halo,

hydroxy, C_{1-5} alkylsulfonyl, C_{1-5} alkylthio, trihaloC_{1-5} alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_{1-5} alkyl, trihaloC_{1-5} alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

R^{160} is hydrogen, C_{1-5} alkyl, phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro, or R^{160} is C_{1-5} alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro;

R^{161} is C_{1-10} alkyl, substituted C_{1-10} alkyl where the substituents are halogen, trihaloC_{1-5} alkyl, C_{1-5} alkoxy, carboxy, C_{1-5} alkoxycarbonyl, amino, C_{1-5} alkylamino, diC_{1-5} alkylamino, diC_{1-5} alkylaminoC_{1-5} alkylamino, C_{1-5} alkylaminoC_{1-5} alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_{1-5} alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_{1-5} alkyl, halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

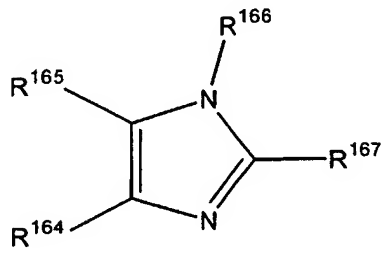
R^{161} is NR^{163} R^{164} where R^{163} and R^{164} are independently selected from hydrogen and C_{1-5} alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_{1-5} alkyl;

R^{162} is hydrogen, C_{1-5} alkyl, nitro, amino, and halogen;

and pharmaceutically acceptable salts thereof.

[000112] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-substituted imidazoles that are

described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII**:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl and halogen, or substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, SEM, C_{1-5} alkoxycarbonyl, aryloxycarbonyl, arylC_{1-5} alkyloxycarbonyl, arylC_{1-5} alkyl, phthalimidoC_{1-5} alkyl, aminoC_{1-5} alkyl, diaminoC_{1-5} alkyl, succinimidoC_{1-5} alkyl, C_{1-5} alkylcarbonyl, arylcarbonyl, C_{1-5} alkylcarbonylC_{1-5} alkyl, aryloxycarbonylC_{1-5} alkyl, heteroarylC_{1-5} alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted arylC_{1-5} alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, C_{1-5} alkoxy, halogen, amino, C_{1-5} alkylamino, and diC_{1-5} alkylamino;

R^{167} is $(A^{11})_n$ -$(CH^{165})_q$ –X^{24} wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{1-5} alkoxy, phenoxy, phenyl, arylC_{1-5} alkyl, amino, C_{1-5} alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, araC_{1-5} alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C_{1-5} alkyl,

wherein the substituents are selected from the group consisting of one or more C_{1-5} alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted C_{1-5} alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

substituted arylC_{1-5} alkyl,

wherein the alkyl substituent is hydroxyl,

substituted arylC_{1-5} alkyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted amido,

wherein the carbonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, arylC_{1-5} alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted C_{1-5} alkylthio,

wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,

substituted C_{1-5} alkylsulfonyl,

wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,

substituted phenylsulfonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_{1-5} alkoxy and trifluoromethyl,

with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl, C_{1-5} alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

if A^{11} is sulfur and q is 1, then X^{24} cannot be C_{1-2} alkyl;

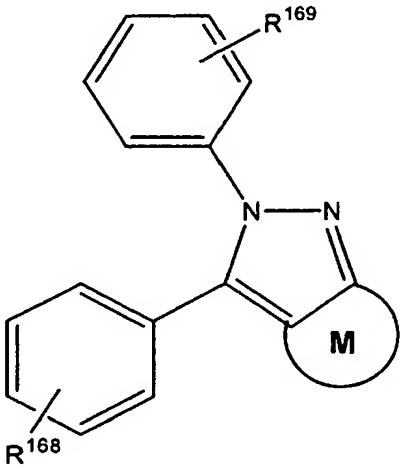
if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl,C_{1-5} alkylsulfonyl or phenylsulfonyl;

if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not SEM (2-(trimethylsilyl)ethoxymethyl);

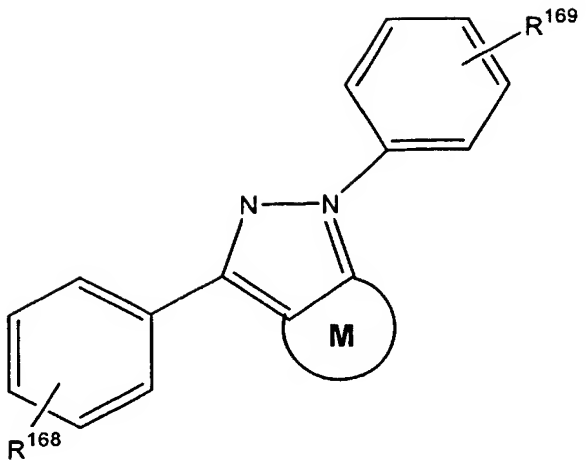
if n is 0 and q is 0, then X^{24} cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

[000113] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



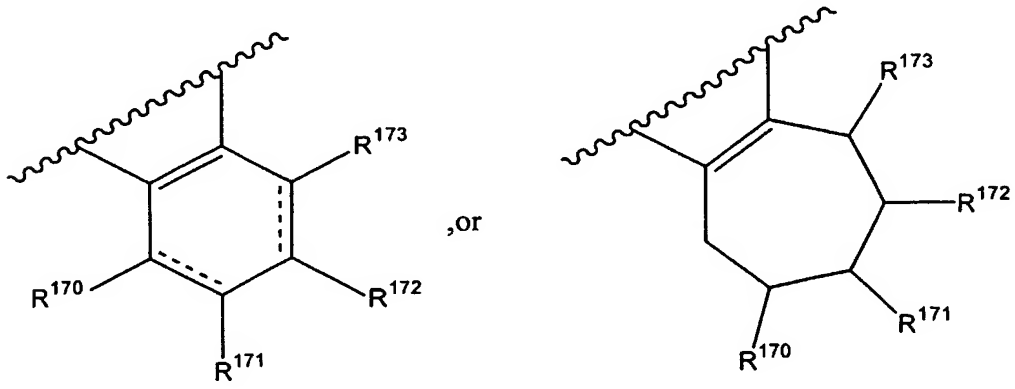
XXXIII



XXXIV

wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, (C_1 -C_6)alkyl, (C_1 -C_6)alkoxy, nitro, amino, hydroxy, trifluoro, —S(C_1 -C_6)alkyl, —SO(C_1 -C_6)alkyl and —SO_2 (C_1 -C_6)alkyl; and the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



wherein:

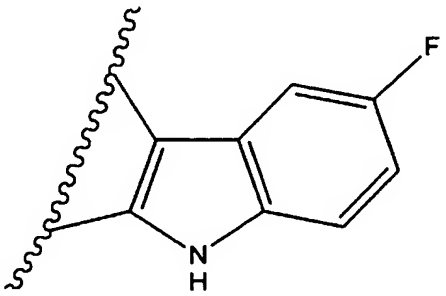
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxy and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of —$OCOCH_2$ —, —$ONH(CH_3)COCH_2$ —, —OCOCH.dbd. and —O—;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, (C_1 -C_6)alkyl, (C_1 -C_6)alkoxy, =NOH, —NR^{174} R^{175}, —OCH_3, —OCH_2 CH_3, —OSO_2 $NHCO_2$ CH_3, =$CHCO_2$ CH_2 CH_3, —CH_2 CO_2 H, —CH_2 CO_2 CH_3, —CH_2 CO_2 CH_2 CH_3, —CH_2 $CON(CH_3)_2$, —CH_2 CO_2 $NHCH_3$, —$CHCHCO_2$ CH_2 CH_3, —$OCON(CH_3)OH$, —$C(COCH_3)_2$, di(C_1 -C_6)alkyl and di(C_1 -C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, (C_1 -C_6)alkyl, (C_1 -C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxy, amino, (C_1 -C_6)alkyl and (C_1 -C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of —O—and



R^{174} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$ and (C_1 -C_6)alkyl; and

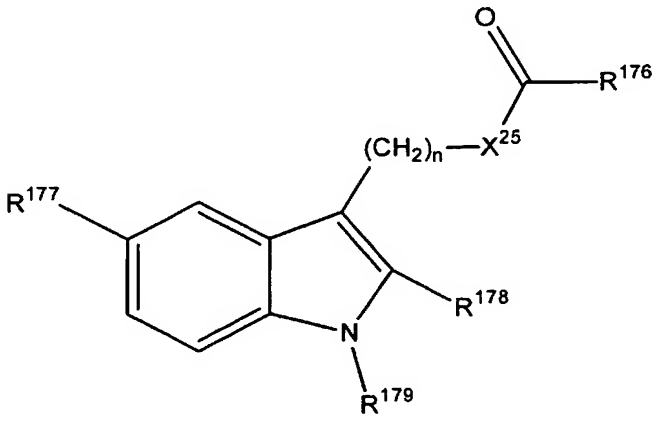
R^{175} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$, (C_1 -C_6)alkyl, —$CONH_2$ and —SO_2 CH_3 ;

with the proviso that

if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[000114] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_8 cycloalkyl, C_1 to C_6 hydroxyalkyl, branched C_1 to C_6 hydroxyalkyl, hydroxy substituted C_4 to C_8 aryl, primary, secondary or tertiary C_1 to C_6 alkylamino, primary, secondary or tertiary branched C_1 to C_6 alkylamino, primary, secondary or tertiary C_4 to C_8 arylamino, C_1 to C_6 alkylcarboxylic acid, branched C_1 to C_6 alkylcarboxylic acid, C_1 to C_6 alkylester, branched C_1 to C_6 alkylester, C_4 to C_8 aryl, C_4 to C_8 arylcarboxylic acid, C_4 to C_8 arylester, C_4 to C_8 aryl substituted C_1 to C_6 alkyl, C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_8 cycloalkyl, C_4 to C_8 aryl, C_4 to C_8 aryl-substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to

C_6 branched alkoxy, C_4 to C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

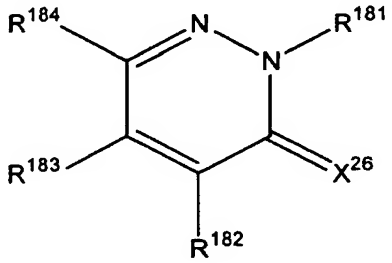
R^{178} is hydrogen, C_1 to C_6 alkyl or C_1 to C_6 branched alkyl;

R^{179} is C_1 to C_6 alkyl, C_4 to C_8 aroyl, C_4 to C_8 aryl, C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 to C_8 aryl-substituted C_1 to C_6 alkyl, alkyl-substituted or aryl-substituted C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 to C_8 aroyl, or alkyl-substituted C_4 to C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N—R^{180}, where R^{180} is C_1 to C_6 alkyl or C_1 to C_6 branched alkyl.

[000115] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



XXXVI

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X^{26} is selected from the group consisting of O, S, —NR^{185}, —NOR^a, and –$NNR^b R^c$;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^a, R^b, and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, —$(CH_2)_n$ $C(O)R^{186}$, —$(CH_2)_n$ $CH(OH)R^{186}$, —$(CH_2)_n$ $C(NOR^d)R^{186}$, —$(CH_2)_n$ $CH(NOR^d)R^{186}$, —$(CH_2)_n$ $CH(NR^d\ R^e)R^{186}$, —R^{187} R^{188}, —$(CH_2)_n$ C□CR^{188}, —$(CH_2)_n$ $[CH(CX^{26'}{}_3)]_m$ $(CH_2)_p$ R^{188}, —$(CH_2)_n$ $(CX^{26'}{}_2)_m$ $(CH_2)_p$ R^{188}, and —$(CH_2)_n$ $(CHX^{26'})_m$ $(CH_2)_m$ R^{188} ;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

n is an integer from 0-10; and

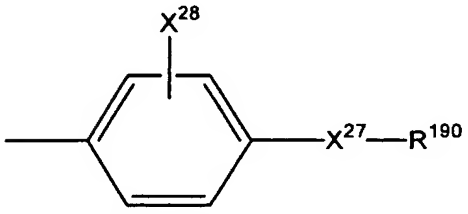
p is an integer from 0-10; and

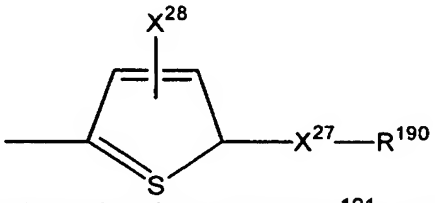
R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl,

carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of:



and


^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, S(O), $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}\ R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, —$NHNH_2$, and —$NCHN(R^{191})R^{192}$;

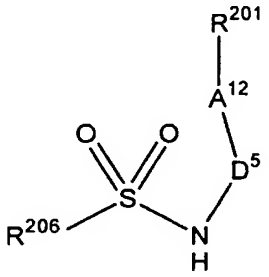
R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

Y^8 is selected from the group consisting of $-OR^{195}$, —SR^{195}, —$C(R^{197})(R^{198})R^{195}$, —$C(O)R^{195}$, —$C(O)OR^{195}$, —$N(R^{197})C(O)R^{195}$, —$NC(R^{197})R^{195}$, and —$N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $NR^{199}\ R^{200}$; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[000116] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



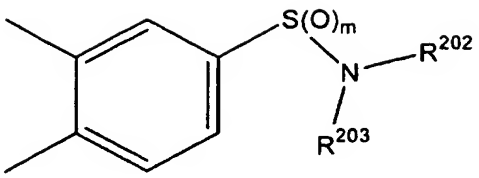
XXXVII

herein:

A^{12} denotes oxygen, sulphur or NH;

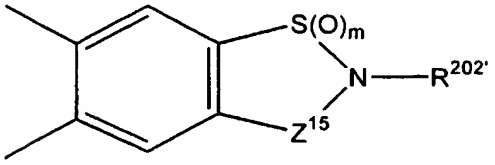
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n -X^{29}$; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n -X^{29}$, $R^{202'}$ denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n -X^{29}$,

wherein:

X^{29} denotes halogen, NO_2, —OR^{204}, —COR^{204}, —$CO_2 R^{204}$, —$OCO_2 R^{204}$, —CN, —$CONR^{204} OR^{205}$, —$CONR^{204} R^{205}$, —SR^{204}, —$S(O)R^{204}$, —$S(O)_2 R^{204}$, —$NR^{204} R^{205}$, —$NHC(O)R^{204}$, —$NHS(O)_2 R^{204}$;

Z^{15} denotes $-CH_2$ —, —$CH_2 -CH_2$ —, —$CH_2 -CH_2 -CH_2$ —, —CH_2 –CH=CH—, —CH=CH—CH_2 —, —CH_2 —CO—, —CO—CH_2 —, —NHCO—, —CONH—, —$NHCH_2$ —, —CH_2 NH—, —N=CH—, —NHCH—, —CH_2–CH_2—NH—, —CH=CH—, >N—R^{203}, >C=O, >$S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

R^{206} is a straight-chained or branched C_{1-4} -alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3;

and the pharmaceutically acceptable salts thereof.

[000117] Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent Nos. 6,169,188, 6,020,343, 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Patent No. 6,359,182 (C-nitroso compounds).

[000118] Cyclooxygenase-2 selective inhibitors that are useful in the present invention can be supplied by any source as long as the cyclooxygenase-2-selective inhibitor is pharmaceutically acceptable. Cyclooxygenase-2-selective inhibitors can be isolated and purified from natural sources or can be synthesized. Cyclooxygenase-2-selective inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[000119] In the present compositions and method, other compounds may also be present in addition to the cyclooxygenase-2 selective inhibitor and the PPARα agonist. For example, a compound such as p38 MAP kinase may optionally be present. It is believed that p38 MAP kinase can phosphorylate PPARα and enhance ligand dependent transactivation. See, *e.g.*, Barger, P. M. *et al., J. Biol. Chem.,* Sept. 27, (2001).

[000120] In an embodiment of the present method, a subject in need of prevention or treatment of pain, inflammation or inflammation-associated disorder is treated with a PPARα agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof. In one embodiment, the subject is treated with an amount of a PPARα agonist and an amount of a Cox-2

selective inhibitor, where the amount of the PPARα agonist and the amount of the Cox-2 selective inhibitor together provide a dosage or amount of the combination that is sufficient to constitute an effective amount of the combination. The effective amount can be a pain or inflammation suppressing treatment or prevention effective amount.

[000121] In another embodiment of the subject method, a subject in need of prevention or treatment of cardiovascular disease or disorder is treated with a PPARα agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof. In one embodiment, the subject is treated with an amount of a PPARα agonist and an amount of a Cox-2 selective inhibitor, where the amount of the PPARα agonist and the amount of the Cox-2 selective inhibitor together provide a dosage or amount of the combination that is sufficient to constitute an effective amount of the combination. The effective amount can be a cardiovascular disorder or disease suppressing treatment or prevention effective amount.

[000122] In another embodiment of the present method, a subject in need of prevention or treatment of cancer is treated with a PPARα agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof. In one embodiment, the subject is treated with an amount of a PPARα agonist and an amount of a Cox-2 selective inhibitor, where the amount of the PPARα agonist and the amount of the Cox-2 selective inhibitor together provide a dosage or amount of the combination that is sufficient to constitute an effective amount of the combination. The effective amount can be a cancer suppressing treatment or prevention effective amount.

[000123] In another embodiment of the subject method, a subject in need of prevention or treatment of Alzheimer's disease is treated with a PPARα agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof. In one embodiment, the subject is treated with an amount of a PPARα agonist and an amount of a Cox-2 selective inhibitor, where the amount of the PPARα agonist and the amount of the Cox-2 selective inhibitor together provide a dosage or amount of the combination that is sufficient

to constitute an effective amount of the combination. The effective amount can be an Alzheimer's disease suppressing treatment or prevention effective amount.

[000124] As used herein, an "effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is readily determined by one or ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be administered to a patient and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used; the nature and severity of the illness to be treated as well as on the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[000125] The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies. The phrase "therapeutically-effective" is to be understood to be equivalent to the phrase "effective for the treatment, prevention, or inhibition", and both are intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in the severity of cancer, Alzheimer's disease, cardiovascular disease, or pain and inflammation and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

[000126] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[000127] In the present method, the amount of the PPARα agonist that is used is such that, when administered with the cyclooxygenase-2 selective inhibitor, it is sufficient to constitute an effective amount of the combination. It is preferred that the dosage of the combination constitute a therapeutically effective amount.

[000128] It is preferred that the amount of the PPARα agonist that is used in combination with a Cox-2 selective inhibitor for a single dosage of treatment is within a range of from about 0.01 mg/kg of body weight of the subject to about 200 mg/kg. It is more preferred that the amount is from about 0.1 mg/kg to about 50 mg/kg, even more preferred that it is from about 1 mg/kg to about 20 mg/kg, and yet more preferred that it is from about 1 mg/kg to about 10 mg/kg.

[000129] The frequency of dose will depend upon the half-life of the PPARα agonist molecule. If the PPARα agonist molecule has a short half life (*e.g.* from about 2 to 10 hours) it may be necessary to give one or more doses per day. Alternatively, if the PPARα agonist molecule has a long half-life (*e.g.* from about 2 to about 15 days) it may only be necessary to give a dosage once per day, per week, or even once every 1 or 2 months. A preferred dosage rate is to administer the dosage amounts described above to a subject once per day.

[000130] For the purposes of calculating and expressing a dosage rate, all dosages that are expressed herein are calculated on an average amount-per-day basis irrespective of the dosage rate. For example, one 100 mg dosage of an ingredient taken once every two days would be expressed as a dosage rate of 50 mg/day. Similarly, the dosage rate of an ingredient where 50 mg is taken twice per day would be expressed as a dosage rate of 100 mg/day.

[000131] For the purposes of calculation of a dosage rate for the present method, the weight of an adult human is assumed to be 70 kg.

[000132] The amount of Cox-2 selective inhibitor that is used in the subject method may be an amount that, when administered with the

PPARα agonist, is sufficient to constitute an effective amount of the combination. Preferably, such amount would be sufficient to provide a therapeutically effective amount of the combination. The therapeutically effective amount can also be described herein as a pain or inflammation suppressing treatment or prevention effective amount of the combination, or as a cardiovascular disorder or disease suppressing treatment or prevention effective amount, or as a cancer suppressing treatment or prevention effective amount, or as an Alzheimer's disease suppressing treatment or prevention effective amount.

[000133] In the present method, the amount of Cox-2 selective inhibitor that is used in the novel method of treatment preferably ranges from about 0.01 to about 100 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more preferably from about 0.1 to about 50 mg/day·kg, even more preferably from about 1 to about 20 mg/day·kg.

[000134] When the Cox-2 selective inhibitor comprises rofecoxib, it is preferred that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more preferably from about 0.18 to about 0.4 mg/day·kg.

[000135] When the Cox-2 selective inhibitor comprises etoricoxib, it is preferred that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more preferably from about 0.8 to about 4 mg/day·kg.

[000136] When the Cox-2 selective inhibitor comprises celecoxib, it is preferred that the amount used is within a range of from about 1 to about 10 mg/day·kg, even more preferably from about 1.4 to about 8.6 mg/day·kg, and yet more preferably from about 2 to about 3 mg/day·kg.

[000137] When the Cox-2 selective inhibitor comprises valdecoxib or parecoxib sodium, it is preferred that the amount used is within a range of from about 0.1 to about 3 mg/day·kg, and even more preferably from about 0.3 to about 1 mg/day·kg.

[000138] In the present method, and in the subject compositions, the PPARα agonist is administered with, or is combined with, a Cox-2 selective inhibitor. It is preferred that the weight ratio of the amount of PPARα agonist to the amount of Cox-2 selective inhibitor that is administered to the subject is within a range of from about 0.0001:1 to about 20,000:1, more preferred is a range of from about 0.02:1 to about 200:1, even more preferred is a range of from about 0.05:1 to about 10:1.

[000139] The combination of a PPARα agonist and a Cox-2 selective inhibitor can be supplied in the form of a novel therapeutic composition that is believed to be within the scope of the present invention. The relative amounts of each component in the therapeutic composition may be varied and may be as described just above. The PPARα agonist and Cox-2 selective inhibitor that are described above can be provided in the therapeutic composition so that the preferred amounts of each of the components are supplied by a single dosage, a single injection or a single capsule for example, or, by up to four, or more, single dosage forms.

[000140] When the novel combination is supplied along with a pharmaceutically acceptable carrier, a pharmaceutical composition is formed. A pharmaceutical composition of the present invention is directed to a composition suitable for the prevention or treatment of pain, inflammation and/or an inflammation-associated disorder, or for the prevention or treatment of a cardiovascular disease or disorder, or for the prevention or treatment of cancer, or for the prevention or treatment of Alzheimer's disease. The pharmaceutical composition comprises a pharmaceutically acceptable carrier, a PPARα agonist, and a cyclooxygenase-2 selective inhibitor.

[000141] Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that

side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

[000142] The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

[000143] The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[000144] Also included in the combination of the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of PPARα agonists and cyclooxygenase-2 selective inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic,

anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

[000145] Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

[000146] The method and combination of the present invention are useful for, but not limited to, the prevention, inhibition, and treatment of pain and/or inflammation in a subject, and for treatment of inflammation-associated disorders, such as for use as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, combinations of the invention would be useful to treat arthritis, including, but not limited to, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such combinations of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, and skin related conditions such as psoriasis, eczema, burns and dermatitis.

[000147] Combinations of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, gastric

ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. Combinations of the invention would be useful in treating inflammation in diseases and conditions such as herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, skin wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, type II diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

[000148] Compositions having the novel combination would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compositions would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compositions would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease. The combinations of the invention are also useful as anti-inflammatory agents, such as for the treatment of arthritis.

[000149] As used herein, the terms "pain, inflammation or inflammation-associated disorder", and "cyclooxygenase-2 mediated disorder" are meant to include, without limitation, each of the symptoms or diseases that is mentioned above.

[000150] Several animal models are available which are appropriate for evaluation of the prevention or treatment of pain and inflammation. See, *e.g.*, Winter *et al., Proc. Soc. Exp. Biol. Med., 111*:544 (1962) for the description of a rat carrageenan foot pad edema test; and Hargreaves *et*

al., Pain 32:77 (1988), for the description of a rat carrageenan-induced analgesia test.

[000151] Animal models for arthritis are also described by Stuart, J., *Ann. Rev. Immunol, 2*:199 (1984). Chinn, K.S. *et al., Lipids, 32(9)*:979 - 988 (1997), describe adjuvant induced arthritis by dietary arachidonic acid in essential fatty acid deficient rats.

[000152] Animal models for Alzheimer's disease are described in U. S. Patent No. 6,310,048, to Kumar, where SAM P8 mice are used to test the effects of agents upon the synthesis of beta-amyloid protein and upon the severity of symptoms similar to those that present with Alzheimer's disease.

[000153] The present method includes the treatment and/or prevention of a cyclooxygenase-2 mediated disorder in a subject, where the method comprises treating the subject having or susceptible to the disorder with a therapeutically-effective amount of a combination of a PPARα agonist and a compound or salt of any of the cyclooxygenase-2 selective inhibitors that are described in this specification. This method is particularly useful where the cyclooxygenase-2 mediated disorder is inflammation, arthritis, pain, or fever.

[000154] The methods and compositions described herein as the subject methods and compositions would be useful for the prevention, treatment or inhibition of cancer. Preferably, the subject methods and compositions of the present invention may be used for the treatment, prevention or inhibition of neoplasia disorders including benign and malignant neoplasias, and neoplasias in metastasis, and also including acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, breast cancer, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal

sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

[000155] Several animal models are available which are appropriate for evaluation of the prevention or treatment of cancer. For example, Petrik, M. B. *et al., J. Nutr., 130(10)*:2434 - 2443 (2000) describe the use of Apc(Min/+) mice as models for testing for intestinal tumorigenesis. Desaulniers, D., *et al., Environ Health Perspect, Jul*:109 (2001) describe the use of rats having mammary tumors initated by methylnitrosourea (MNU) as test subjects. Moser, A. R., *et al., Cancer Tes. 61(8)*:3480 - 3485 (2001) describes the use of Apc(min)/+ mice having mammary tumors initiated by ethylnitrosourea (ENU) as model test animals.

[000156] The compositions and methods described herein would be useful for, but not limited to, the prevention, treatment or inhibition of cardiovascular disease or disorder in a subject in need of such prevention,

treatment or inhibition. Such diseases and disorders may also be referred to herein as "cardiovascular/metabolic diseases and disorders" or "CVMDs". Preferably, the compositions and methods described herein would be useful for the prevention, treatment or inhibition of inflammation-related cardiovascular disorders in a subject in need of such prevention, treatment or inhibition. The compositions and methods would be useful for prevention of coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including *Chlamydia*-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

[000157] Several animal models are available which are appropriate for evaluation of prevention of cardiovascular conditions including the prevention of atherosclerosis. See, *e.g.,* Stehbens, *Prog. Card. Dis., XXIX,* 1007-28 (1986), and Zhang *et al., Science, 258:* 468-71 (1992).

[000158] An ApoE mouse model for atherosclerosis has been described by Roselear *et al.* (*Arterioscle. Thromb. Vasc. Biol., 16*, 1013-18 (1996)). The cyclooxygenasse-2 inhibitor should be active, at a dose of 20 mg/kg, in preventing atherosclerotic lesions. Hasty, A. H., *et al., J. Biol. Chem., 276(40)*:37402 - 37408 (2001), describe the use of doubly mutant mice (LDLR-/-;ob/ob) as test models for hpercholesterolemia, hypertriglyceridemia, and atherosclerosis.

[000159] As described above, an embodiment of the present invention comprises a pharmaceutical composition for the prevention of cardiovascular disorders, comprising a therapeutically-effective amount of a combination of a PPARα agonist and a cyclooxygenase-2 selective inhibitor in association with at least one pharmaceutically-acceptable

carrier, adjuvant or diluent and, if desired, other active ingredients. There are large numbers of cardiovascular treatment agents available in commercial use, in clinical evaluation and in pre-clinical development, which could be selected for use with the subject combination for the prevention of cardiovascular disorders by combination drug therapy. Such agent can be one or more agents selected from, but not limited to several major categories, namely, a lipid-lowering drug, including an IBAT inhibitor, niacin, a statin, a CETP inhibitor, and a bile acid sequestrant, an anti-oxidant, including vitamin E and probucol, a IIbIIIa antagonist (including xemilofiban and orbofiban), an aldosterone inhibitor (including spirolactone and epoxymexrenone), an AII antagonist (including losartan), a β-blocker, aspirin, a loop diuretic and an ACE inhibitor.

[000160] In particular, combinations of the present invention are useful for the treatment of diseases or disorders that are mediated by the activity of PPARα. Examples of diseases or disorders that are mediated by the activity of PPARα include, without limitation, hyperglycaemia, hyperlipidaemia, atherosclerosis. ischemic heart diseases, age-related disorders, dyslipidemia, insulin resistance, chronic inflammation, predisposition to atherosclerosis, tumorigenesis, hepatocarcinogenesis, atheromatous diseases, diabetes mellitus, hyperglycemia, obesity, hyperlipidemia, hypertriglyveridemia, hypercholesteremia, raising HDL levels, vascular restinosis, irritable bowel syndrome, pancreatitis, abdominal obesity, adipose cell tumors, adipose cell carcinomas, liposarcoma, disorders where insulin resistance is a component, Syndrome X, ovarian hyperandrogenism, obesity, hypoalphalipoproteinemia, type II diabetes, vascular disease, and skin wound healing.

[000161] The terms "treating" or "to treat" mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of cancer, Alzheimer's disease, cardiovascular disease or disorder, or pain and/or

inflammation associated with, but not limited to, any of the diseases or disorders described herein. Besides being useful for human treatment, these combinations are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

[000162] The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of, or who has cancer, Alzheimer's disease, cardiovascular disease, or pain, inflammation and/or any one of the known inflammation-associated disorders. The subject is typically a mammal. "Mammal", as that term is used herein, refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc., Preferably, the mammal is a human.

[000163] For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of prevention and/or treatment of cancer, Alzheimer's disease, cardiovascular disease, or pain, inflammation and/or an inflammation-associated disorder. The subject may be a human subject who is at risk for cancer, Alzheimer's disease, cardiovascular disease, or pain and/or inflammation, or for obtaining an inflammation-associated disorder, such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-causing agents, exposure to pathogenic agents and the like.

[000164] The subject pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[000165] The phrases "combination therapy", "co-administration", "administration with", or "co-therapy", in defining the use of a cyclooxygenase-2 selective inhibitor agent and a PPARα agonist, is

intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule or dosage device having a fixed ratio of these active agents or in multiple, separate capsules or dosage devices for each agent, where the separate capsules or dosage devices can be taken together contemporaneously, or taken within a period of time sufficient to receive a beneficial effect from both of the constituent agents of the combination.

[000166] Although the combination of the present invention may include administration of a PPARα agonist component and a cyclooxygenase-2 selective inhibitor component within an effective time of each respective component, it is preferable to administer both respective components contemporaneously, and more preferable to administer both respective components in a single delivery dose.

[000167] In particular, the combinations of the present invention can be administered orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be

uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[000168] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[000169] Aqueous suspensions can be produced that contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000170] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[000171] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid

paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol.

[000172] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[000173] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[000174] Syrups and elixirs containing the novel combination may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[000175] The subject combinations can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above, or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

[000176] The subject combination can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

[000177] The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

[000178] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

[000179] Various delivery systems include capsules, tablets, and gelatin capsules, for example.

[000180] The present invention further comprises kits that are suitable for use in performing the methods of treatment, prevention or inhibition described above. In one embodiment, the kit contains a first dosage form comprising a PPARα agonist in one or more of the forms identified above and a second dosage form comprising one or more of the cyclooxygenase-2 selective inhibitors or prodrugs thereof identified above, in quantities sufficient to carry out the methods of the present invention. Preferably, the first dosage form and the second dosage form together comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder, or of cardiovascular disease or disorder, or of cancer, or of Alzheimer's disease.

[000181] The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification,

together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

COMPARATIVE EXAMPLE 1

[000182] This example shows the preparation of celecoxib.

[000183] Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

[000184] Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

[000185] Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

[000186] To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of $C_{17}H_{14}N_3O_2SF_3$; C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

[000187] This illustrates the production of a composition containing celecoxib and fenofibrate, and of a pharmaceutical composition containing the combination.

[000188] Fenofibrate is available under the trade name TRICOR® from Abbott Laboratories, North Chicago, IL. Celecoxib can be prepared as described in Comparative Example 1, or it can be obtained under the trade name CELEBREX® from Pharmacia Corporation, Peapack, NJ.

[000189] A therapeutic composition of the present invention can be formed by intermixing fenofibrate (160 g, available as TRICOR®, from Abbott Laboratories), and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Comparative Example 1, or as available from Pharmacia Corporation, Peapack, NJ), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the two compounds. After mixing, the combination of celecoxib and pioglitazone form a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 160 mg of fenofibrate and about 200 mg of celecoxib.

[000190] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains 160 mg of fenofibrate and 200 mg celecoxib.

[000191] Alternatively, the fenofibrate and the celecoxib may be dissolved into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to provide 160 mg of pioglitazone and 200 mg of celecoxib.

[000192] Therapeutic and pharmaceutical compositions comprising a combination of any of the cyclooxygenase-2 selective inhibitors and any of the sources of PPARα agonists that are described above can be formed by similar methods.

EXAMPLE 3

[000193] This illustrates the evaluation of the biological efficacy of a therapeutic composition of fenofibrate and celecoxib for the alleviation of pain and inflammation.

[000194] A therapeutic composition containing fenofibrate and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by a rat carrageenan foot pad edema test and by a rat carrageenan-induced analgesia test.

Rat Carrageenan Foot Pad Edema Test:

[000195] The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter, *et al.*, (*Proc. Soc. Exp. Biol. Med., 111*, 544 (1962)). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over sixteen hours prior to the test. The rats are dosed orally (1 mL) with compounds of Example 2 suspended in a carrier vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with only the carrier vehicle alone. One hour later, a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered to one foot and the volume of the injected foot is measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema is determined (Otterness and Bliven, Laboratory Models for Testing NSAIDS, in *Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The percent inhibition shows the percent decrease from control paw volume determined in this procedure. It is believed that the data

would show that the combination of fenofibrate and celecoxib provides effective anti-inflammatory activity.

Rat Carrageenan-induced Analgesia Test:

[000196] The analgesia test using rat carrageenan is performed with materials, reagents and procedures essentially as described by Hargreaves, *et al.*, (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats are treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats are placed in a special PLEXIGLAS® container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty-minute period, thermal stimulation is begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell will turn off the lamp and timer when the light is interrupted by paw withdrawal. The time until the rat withdraws its foot is then measured. The withdrawal latency in seconds is determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal is determined. It is believed that results would show that a combination of fenofibrate and celecoxib provides effective analgesic activity.

EXAMPLE 4

[000197] This illustrates the biological efficacy of a therapeutic composition of fenofibrate and celecoxib for the treatment of collagen-induced arthritis in mice.

[000198] A therapeutic composition containing fenofibrate and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by induction and assessment of collagen-induced arthritis in mice.

[000199] Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 μg of chick-type II collagen (CII) in complete Freunds adjuvant (Sigma) on day 0 at the base of the tail as described in [J. Stuart, *Annual Rev. Immunol.*, 2, 199 (1984)]. Compounds are prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, Mo.), and 0.025% Tween 20 (Sigma). The cyclooxygenase-2 inhibitor (celecoxib, as

described in Comparative Example 1), and fenofibrate (available under the trade name TRICOR® from Abbott Laboratories, North Chicago, IL) are administered alone or in combination as a therapeutic composition as described in Example 2. The compounds are administered in non-arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55. Animals are boosted on day 21 with 50 μg of collagen (CII) in incomplete Freunds adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as described in P. Wooley, *et al., Trans. Proc., 15*, 180 (1983). The animals are measured for incidence of arthritis and severity in the animals where arthritis was observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, *i.e.*, no redness or swelling are scored 0. Any redness or swelling of digits or the paw are scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

Histological Examination of Paws:

[000200] In order to verify the gross determination of a non-arthritic animal, a histological examination can be performed. Paws from animals sacrificed at the end of the experiment are removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods, 88*, 109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

[000201] It is believed that results will show that the combination of a cyclooxygenase-2 selective inhibitor with the PPARα agonist fenofibrate was an efficacious treatment for collagen-induced arthritis in mice.

[000202] It is believed that Examples 3 and 4 can be repeated with compositions comprising any of the PPARα agonists in combination with any of the cyclooxygenase-2 selective inhibitors that are described herein, with the results showing that the combination provides effective anti-inflammatory activity, effective analgesic activity, and is an efficacious treatment of collagen-induced arthritis in mice.

EXAMPLE 5

[000203] This example illustrates the efficacy of a combination of celecoxib and fenofibrate in alleviating adjuvant induced arthritis in rats.

[000204] A combination of celecoxib and fenofibrate can be prepared by the methods described in Example 2. The efficacy of the combination can be tested by the method described by Chinn, K. S. *et al.*, in *Lipids, 32(9)*:979 - 988 (1997).

[000205] It is believed that the subject combination would be found to be effective in alleviating adjuvant induced arthritis in rats. In fact, it is believed that a combination that included any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein would also be effective for such purpose.

EXAMPLE 6

[000206] This example illustrates the efficacy of a PPARα agonist in combination with a cyclooxygenase-2 selective inhibitor for the treatment of cancer.

[000207] A combination of any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein can be prepared by the methods described in Example 2. The efficacy of the combination can be tested by the methods described in U.S. Patent No. 6,242,196, for:

a. the reduction in size of adipose cell tumors *in vivo*;
b. the inhibition of proliferation of leukemic cells; and
c. the inhibition of proliferation of prostate cancer cells.

[000208] It is believed that the subject combinations would be found to be effective in reducing the size of adipose cell tumors *in vivo*; in inhibiting the proliferation of leukemic cells; and in inhibiting the proliferation of prostate cancer cells.

EXAMPLE 7

[000209] This example illustrates the efficacy of a combination of celecoxib and fenofibrate in preventing or treating intestinal tumors in Apc (Min/+) mice.

[000210] A combination of celecoxib and fenofibrate can be prepared by the methods described in Example 2. The efficacy of the combination in preventing or reducing intestinal tumorigenesis in Apc (Min/+) mice can be tested by the method described by Petrik, M. B. H. *et al.*, in *J. Nutr., 130*:2434 - 2443 (2000).

[000211] It is believed that the subject combination would be found to be effective in preventing or reducing tumoregenesis in such mice. In fact, it is believed that a combination that included any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein would also be effective for such purpose.

EXAMPLE 8

[000212] This example illustrates the efficacy of a combination of celecoxib and fenofibrate in preventing or treating mammary hyperplasias and carcinomas in Apc(min/+) mice.

[000213] A combination of celecoxib and fenofibrate can be prepared by the methods described in Example 2. The efficacy of the combination for the prevention or treatment of mammary hyperplasias and carcinomas in mice can be tested by the method described by Moser, A. R. *et al., Cancer Res., 61(8)*:3480 - 3485 (2001), (for cancers induced by ethylnitrosourea (ENU)), or in rats by the method described by Deasulniers, D. *et al., Environ. Health Perspect., 109(7)*:739 - 747 (2001), (for cancers induced by methylnitrosourea (MNU)).

[000214] It is believed that the subject combination would be found to be effective in prevention or treating mammary tumor development in mice and rats. In fact, it is believed that a combination that included any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein would also be effective for such purpose.

EXAMPLE 9

[000215] This example illustrates the efficacy of a PPARα agonist in combination with a cyclooxygenase-2 selective inhibitor for the improvement of cardiac function in myocardial infarction.

[000216] A combination of any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein can be prepared by the methods described in Example 2. The efficacy of the combination can be tested by the methods described by Saito, T. *et al.*, in *Biochem. and Biophys. Res. Communic., 273*:772 - 775 (2000), for the improvement of cardiac function in myocardial infarction. It is believed that the subject combinations would be found to be effective in improving cardiac function in myocardial infarction.

EXAMPLE 10

[000217] This example illustrates the efficacy of a combination of celecoxib and fenofibrate in preventing or treating hypercholesterolemia, hypertriglyceridemia and atherosclerosis in mice.

[000218] A combination of celecoxib and fenofibrate can be prepared by the methods described in Example 2. The efficacy of the combination for the prevention or treatment of hypercholesterolemia, hypertriglyceridemia and atherosclerosis in mice can be tested by the method described by Hasty, A. H. *et al., J. Biol. Chem., 276(40)*:37402 - 37408 (2001). The method uses doubly mutant LDLR-/-;ob/ob mice as the model animal.

[000219] It is believed that the subject combination would be found to be effective in preventing and/or treating hypercholesterolemia, hypertriglyceridemia and atherosclerosis in mice. In fact, it is believed that

a combination that included any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein would also be effective for such purpose.

EXAMPLE 11

[000220] This example illustrates the efficacy of a combination of celecoxib and fenofibrate in reducing cardiovascular risk in humans.

[000221] A combination of celecoxib and fenofibrate can be prepared by the methods described in Example 2. The efficacy of the combination can be tested by the methods described in any one of the references cited in Table 1, of the publication by Robins, S. J., in *J. Cardiovascular Risk, 8*:195 - 201 (2001).

[000222] It is believed that the subject combination would be found to be effective in reducing cardiovascular risk in humans. In fact, it is believed that a combination that included any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein would also be effective for such purpose.

EXAMPLE 12

[000223] This example illustrates the efficacy of a combination of celecoxib and fenofibrate in preventing or treating diabetes in rats.

[000224] A combination of celecoxib and fenofibrate can be prepared by the methods described in Example 2. The efficacy of the combination for the prevention or treatment of type 2 diabetes in Zucker diabetic fatty rats (ZDF) can be tested by the method described by Shibata, T. *et al.*, in *Br. J. Pharmacol., 130(3)*:495 - 504 (2000).

[000225] It is believed that the subject combination would be found to be effective in preventing and/or treating type 2 diabetes in rats. In fact, it is believed that a combination that included any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein would also be effective for such purpose.

EXAMPLE 13

[000226] This example illustrates the efficacy of a combination of celecoxib and fenofibrate in preventing or treating Alzheimer's disease in mice.

[000227] A combination of celecoxib and fenofibrate can be prepared by the methods described in Example 2. The efficacy of the combination can be tested for the ability to prevent or treat the production and accumulation of amyloid beta protein and for the ability to prevent or alleviate Alzheimer's disease-type symptoms in SAM P8 mice by the method described in U.S. Patent No. 6,310,048 to Kumar.

[000228] It is believed that the subject combination would be found to be effective in preventing and/or treating Alzheimer's disease in mice. In fact, it is believed that a combination that included any one or more of the PPARα agonists that are described herein with any one or more of the cyclooxygenase-2 selective inhibitors that are described herein would also be effective for such purpose.Alzheimer's disease, 6,310,048 to Kumar

[000229] All references cited in this specification, including without limitation, all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000230] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000231] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A method for the prevention, treatment, or inhibition of pain, inflammation, or inflammation-related disorder, or cancer, or Alzheimer's disease, or cardiovascular disease or disorder in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

2. The method according to claim 1, wherein the method is for the treatment of pain, inflammation, or inflammation-related disorder in a subject in need of such treatment, prevention, or inhibition.

3. The method according to claim 1, wherein the peroxisome proliferator activated receptor-α agonist comprises a material that is selected from the group consisting of WY-14,643, medium and long chain fatty acids which are capable of activating PPARα, fibric acid derivatives, fibrates, clofibrate, clofibride, fenofibrate, benzafibrate, ciprofibrate, beclofibrate (beclobrate), etofibrate, simfibrate, gemfibrozil, arylthiazolidinedione derivatives which are capable of activating PPARα, pioglitazone, benzafibrate (bezafibrate), (-) DRF2725, BM-17.0744, omega-3-fatty acids which are capable of activating PPARα, docosahexanoic acid, JTT-501, trichloroacetate, dichloroacetate, DHEA-S, unsaturated C:18 fatty acids which are capable of activating PPARα, arachidonic acid, leukotriene B4, fatty aryls which are capable of activating PPARα, and mixtures thereof.

4. The method according to claim 1, wherein the peroxisome proliferator activated receptor-α agonist comprises a material that is selected from the group consisting of WY-14,643, medium and long chain fatty acids which are capable of activating PPARα, fibric acid derivatives, fibrates, clofibrate, clofibride, fenofibrate, benzafibrate, ciprofibrate, beclofibrate (beclobrate), etofibrate, simfibrate, gemfibrozil, benzafibrate (bezafibrate), (-) DRF2725, BM-17.0744, omega-3-fatty acids which are capable of activating PPARα, JTT-501, trichloroacetate, dichloroacetate,

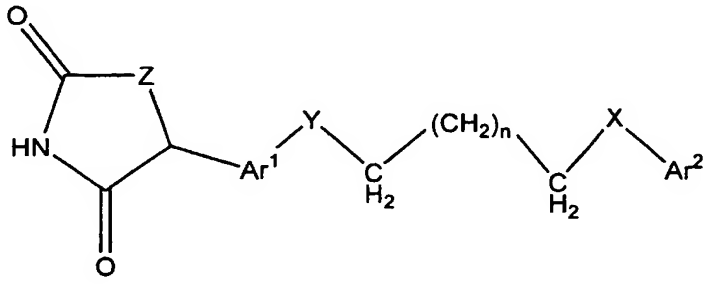
DHEA-S, unsaturated C:18 fatty acids which are capable of activating PPARα, arachidonic acid, leukotriene B4, fatty aryls which are capable of activating PPARα, and mixtures thereof.

5. The method according to claim 1, wherein the peroxisome proliferator activated receptor-α agonist comprises a fibrate.

6. The method according to claim 1, wherein the peroxisome proliferator activated receptor-α agonist comprises a compound selected from the group consisting of WY-14,643, clofibrate, clofibride, fenofibrate, benzafibrate, ciprofibrate, beclofibrate (beclobrate), etofibrate, simfibrate, gemfibrozil, and mixtures thereof.

7. The method according to claim 1, wherein the peroxisome proliferator activated receptor-α agonist comprises a compound that is selected from the group consisting of (-) DRF2725, BM-17.0744, docosahexanoic acid, JTT-501, and mixtures thereof.

8. The method according to claim 1, wherein the peroxisome poroliferator-activated receptor-γ comprises a compound are having the structure:



wherein

Ar^1 is (1) arylene or

(2) heteroarylene,

wherein arylene and heteroarylene are optionally substituted with from 1 to 4 groups selected from R^a;

Ar^2 is (1) ortho-substituted aryl or

(2) ortho-substituted heteroaryl,

wherein said ortho substituent is selected from R;
and aryl and heteroaryl are optionally further substituted with from 1 - 4 groups independently selected from R^a;

X and Y are independently O, S, N-R^b, or CH_2;

Z is O or S;

n is 0 to 3;

R is (1) C_{3-10} alkyl optionally substituted with 1 - 4 groups selected from halo and C_{3-6} cycloalkyl,
(2) C_{3-10} alkenyl, or
(3) C_{3-8} cycloalkyl;

R^a is (1) C_{1-5} alkanoyl,
(2) C_{1-5} alkyl,
(3) C_{2-15} alkenyl,
(4) C_{2-15} alkynyl,
(5) halo,
(6) OR^b,
(7) aryl, or
(8) heteroaryl,
wherein said alkyl, alkenyl, alkynyl, and alkanoyl are optionally substituted with from 1-5 groups selected from R^c, and said aryl and heteroaryl optionally substituted with 1 to 5 groups selected from R^d;

R^b is (1) hydrogen,
(2) C_{1-10} alkyl,
(3) C_{2-10} alkenyl,
(4) C_{2-10} alkynyl,
(5) aryl,
(6) heteroaryl,
(7) aryl C_{1-15} alkyl,
(8) heteroaryl C_{1-5} alkyl,
(9) C_{1-5} cycloalkyl,
(10) C_{3-8} cycloalkyl,

wherein alkyl, alkenyl, alkynyl are optionally substituted with one to four substituents independently selected from R^c, and cycloalkyl, aryl, and heteroaryl are optionally substituted with one to four substituents independently selected from R^d; or

R^c is (1) halo,

(2) aryl,

(3) heteroaryl,

(4) CN,

(5) NO_2,

(6) OR^f,

(7) $S(O)_mR^f$, m=0, 1 or 2, provided that R^f is not H when m is 1 or 2;

(8) NR^fR^f,

(9) NR^fCOR^f,

(10) $NR^fCO_2R^f$,

(11) $NR^fCON(R^f)_2$,

(12) $NR^fSO_2R^f$, provided that

R^f is not H,

(13) COR^f,

(14) CO_2R^f,

(15) $CON(R^f)_2$,

(16) $SO_2N(R^f)_2$,

(17) $OCON(R^f)_2$, or

(18) C_{3-8} cycloalkyl,

wherein said cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 3 groups of halo or C_{1-6} alkyl;

R^d is (1) a group selected from R^c,

(2) C_{1-10} alkyl,

(3) C_{2-10} alkenyl,

(3) C_{2-10} alkenyl,

(4) C_{2-10} alkynyl,

(5) aryl C_{1-10} alkyl, or

(6) heteroaryl C_{1-10} alkyl,

wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl are optionally substituted with a group independently selected from R^e;

R^e is (1) halogen,

(2) amino,

(3) carboxyl,

(4) C_{1-4} alkyl,

(5) C_{1-4} alkoxy,

(6) hydroxy,

(7) aryl,

(8) aryl C_{1-4} alkyl, or

(9) aryloxy;

R^f is (1) hydrogen,

(2) C_{1-10} alkyl,

(3) C_{2-10} alkenyl,

(4) C_{2-10} alkynyl,

(5) aryl,

(6) heteroaryl,

(7) aryl C_{1-15} alkyl,

(8) heteroaryl C_{1-15} alkyl,

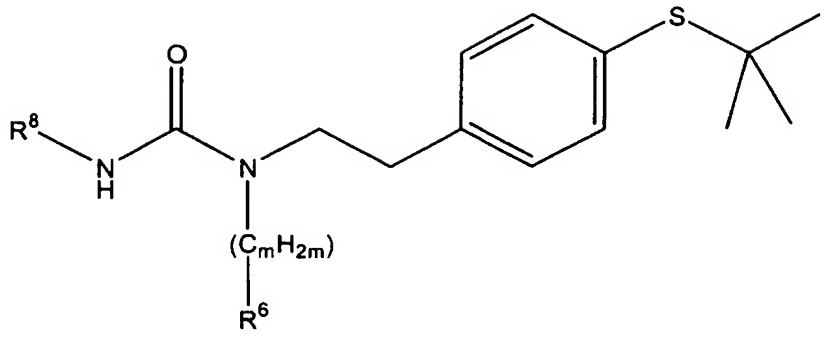
(9) C_{1-15} alkanoyl,

(10) C_{3-8} cycloalkyl;

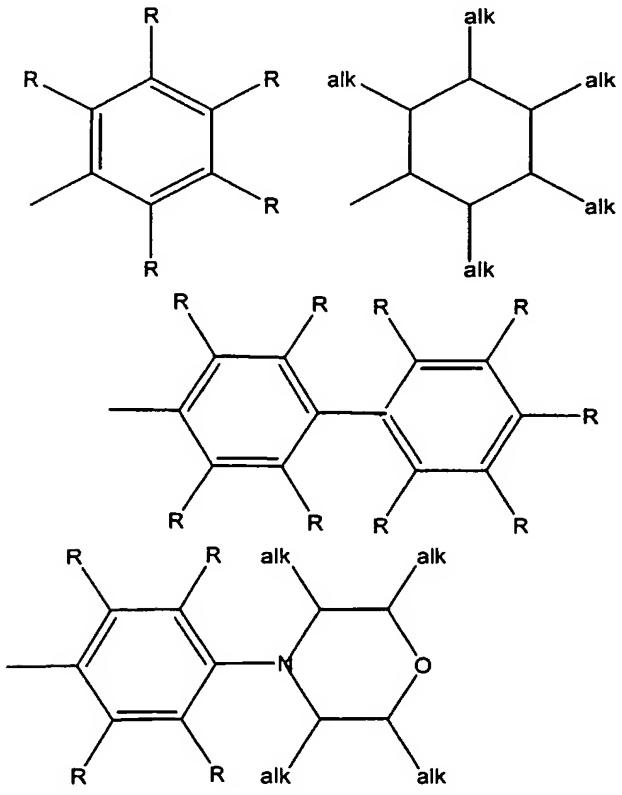
wherein alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkanoyl and cycloalkyl are optionally substituted with one to four groups selected from R^e;

or a pharmaceutically acceptable salt thereof.

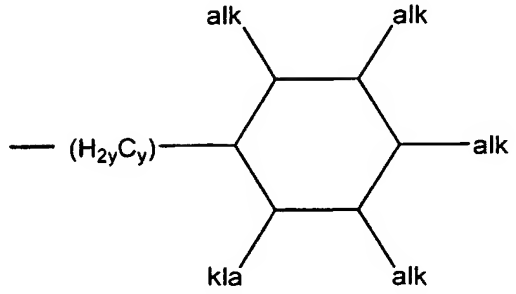
9. The method according to claim 1, wherein the peroxisome proliferator activated receptor-α agonist comprises a compound having the general structure:

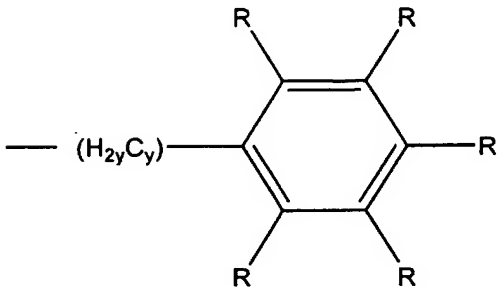


wherein m is from 0 to 20, R^6 is selected from the group consisting of hydrogen and



and R^8 is selected from the group consisting of





where y is 0, 1, or 2, each alk is independently hydrogen or alkyl group containing 1 to 6 carbon atoms, each R group is independently hydrogen, halogen, cyano, --NO_2, phenyl, straight or branched alkyl or fluoroalkyl containing 1 to 6 carbon atoms and which can contain hetero atoms such as nitrogen, oxygen, or sulfur and which can contain functional groups such as ketone or ester, cycloalkyl containing 3 to 7 carbon atoms, or two R groups bonded to adjacent carbon atoms can, together with the carbon atoms to which they are bonded, form an aliphatic or aromatic ring or multi ring system, and where each depicted ring has no more that 3 alk groups, or a salt thereof.

10. The method according to claim 9, wherein the peroxisome proliferator activated receptor-α agonist comprises a compound selected from the group consisting of :

2-(4-(2-(1-(4-biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid,

2-(4-(2-(1-(2-(4-morpholinophenyl)ethyl-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid;

2-(4-(2-(1-(cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid;

2-(4-(2-(1-heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenylthio)-2-methylpropionic acid;

2-(4-(2-(1-(2-chloro-4-(2-trifluoromethylphenyl)phenylmethyl)-3-(cyclohexyl)ureido)ethyl)phenylthio)-2-methylpropionic acid,

salts of said compounds, and mixtures thereof.

11. The method according to claim 1, wherein the method of treatment includes treating the subject with a compound selected from the group consisting of p38 MAP kinase and a PPARα inhibitor.

12. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-2 IC_{50} of less than about 0.2 μmol/L.

13. The method according to claim 11, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-1 IC_{50} of at least about 1 μmol/L.

14. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, parecoxib, lumiracoxib, SD-8381, ABT-963, BMS-347070, and NS-398.

15. The method according to claim 14, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, parecoxib, and lumiracoxib.

16. The method according to claim 15, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, and parecoxib.

17. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises celecoxib.

18. The method according to claim 2, wherein the amount of peroxisome proliferator activated receptor-α agonist, together with the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof,

constitute an amount effective for the treatment, prevention, or inhibition of the pain, inflammation or inflammation-associated disorder.

19. The method according to claim 1, wherein the amount of peroxisome proliferator activated receptor-α agonist is within a range of from about 0.1 to about 50 mg/day per kg of body weight of the subject.

20. The method according to claim 19, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range of from about 0.01 to about 100 mg/day per kg of body weight of the subject.

21. The method according to claim 20, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range of from about 1 to about 20 mg/day per kg of body weight of the subject.

22. The method according to claim 1, wherein the weight ratio of the amount of peroxisome proliferator activated receptor-α agonist to the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof that is administered to the subject is within a range of from about 0.02:1 to about 200:1.

23. The method according to claim 22, wherein the weight ratio of the amount of peroxisome proliferator activated receptor-α agonist to the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof that is administered to the subject is within a range of from about 0.05:1 to about 10:1.

24. The method according to claim 2, wherein the pain, inflammation or inflammation associated disorder is selected from the group consisting of headache, fever, arthritis, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis,

cancer, colorectal cancer, herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, type II diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, ophthalmic diseases, retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue, pulmonary inflammation, nervous system disorders, cortical dementias, and Alzheimer's disease.

25. The method according to claim 2, wherein the pain, inflammation or inflammation associated disorder is an opthalmic disease or opthalmic injury.

26. The method according to claim 25, wherein the opthalmic disease or opthalmic injury is selected from the group consisting of retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue,

27. The method according to claim 24, wherein the pain, inflammation or inflammation associated disorder is arthritis.

28. The method according to claim 27, wherein the arthritis is osteoarthritis.

29. The method according to claim 27, wherein the arthritis is rheumatoid arthritis.

30. The method according to claim 1, wherein the subject is an animal.

31. The method according to claim 30, wherein the subject is a human.

32. The method according to claim 1, wherein the treating step comprises administering a peroxisome proliferator activated receptor-α

agonist and a cycloxoygenase-2 selective inhibitor to the subject enterally or parenterally in one or more dose per day.

33. The method according to claim 32, wherein the peroxisome proliferator activated receptor-α agonist and the cycoloxygenase-2 selective inhibitor are administered to the subject substantially simultaneously.

34. The method according to claim 32, wherein the peroxisome proliferator activated receptor-α agonist and the cycoloxygenase-2 selective inhibitor are administered sequentially.

35. A method for the treatment or prevention of disorders having an inflammatory component in a subject in need of the treatment or prevention of disorders having an inflammatory component, the method comprising administering to the subject a therapeutically effective dose of a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof

36. A composition for the treatment, prevention, or inhibition or pain, inflammation, or inflammation-associated disorder comprising a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

37. The composition according to claim 36, comprising in addition a compound selected from the group consisting of p38 MAP kinase and a PPARα inhibitor.

38. The composition according to claim 36, wherein the composition is useful for treating a subject in need of treatment, prevention, or inhibition of pain, inflammation, or an inflammation-associated disorder, and wherein a dose of the composition constitutes an amount of peroxisome proliferator activated receptor-α agonist and an amount of a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof which together constitute a pain or inflammation suppressing treatment or prevention effective amount.

39. A pharmaceutical composition comprising a peroxisome proliferator activated receptor-α agonist; a cyclooxygenase-2 selective inhibitor or prodrug thereof; and a pharmaceutically-acceptable excipient.

40. A kit that is suitable for use in the treatment, prevention or inhibition of pain, inflammation or inflammation-associated disorder, the kit comprises a first dosage form comprising a peroxisome proliferator activated receptor-α agonist and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the combination of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

41. A method for the treatment, prevention, or inhibition of cardiovascular disease or disorder in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator-activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

42. The method according to claim 61, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, parecoxib, lumiracoxib, SD-8381, ABT-963, BMS-347070, and NS-398.

43. The method according to claim 42, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, parecoxib, and lumiracoxib.

44. The method according to claim 43, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, and parecoxib.

45. The method according to claim 41, wherein the cyclooxygenase-2 selective inhibitor comprises celecoxib.

46. The method according to claim 41, wherein the cardiovascular disease or disorder is selected from the group consisting of

coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation, *Chlamydia*-induced inflammation, viral induced inflammation, inflammation associated with surgical procedures, vascular grafting, coronary artery bypass surgery, revascularization procedures, angioplasty, stent placement, endarterectomy, and inflammation associated with other invasive procedures involving arteries, veins and capillaries.

47. A composition for the treatment, prevention, or inhibition of cardiovascular disease or disorder comprising a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

48. A kit that is suitable for use in the treatment, prevention, or inhibition of cardiovascular disease or disorder, wherein the kit comprises a first dosage form comprising a peroxisome proliferator activated receptor-α agonist and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of cardiovascular disease or disorder.

49. A method for the treatment, prevention, or inhibition of cancer in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator-activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

50. The method according to claim 49, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, parecoxib, lumiracoxib, SD-8381, ABT-963, BMS-347070, and NS-398.

51. The method according to claim 50, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, parecoxib, and

lumiracoxib.

52. The method according to claim 51, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, and parecoxib.

53. The method according to claim 49, wherein the cyclooxygenase-2 selective inhibitor comprises celecoxib.

54. The method according to claim 49, wherein the cancer is selected from the group consisting of neoplasia disorders, benign neoplasias, neoplasias in metastasis, malignant neoplasias, acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, breast cancers and hyperplasias, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor,

squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

55. A composition for the treatment, prevention, or inhibition of cancer comprising a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

56. A kit that is suitable for use in the treatment, prevention, or inhibition of cancer, wherein the kit comprises a first dosage form comprising a peroxisome proliferator activated receptor-α agonist and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of cancer.

57. A method for the prevention, treatment, or inhibition of diseases or disorders that are mediated by the activity of PPARα in a subject that is in need of such prevention, treatment or inhibition, the method comprising administering to the subject a combination of a peroxisome proliferator activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or prodrug thereof, where the amounts of the two materials together comprise an effective amount of the combination.

58. The method according to claim 57, wherein the disease or disorder that is mediated by the activity of PPARα is selected from the group consisting of hyperglycaemia, hyperlipidaemia, atherosclerosis. ischemic heart diseases, age-related disorders, dyslipidemia, insulin resistance, chronic inflammation, predisposition to atherosclerosis, tumorigenesis, hepatocarcinogenesis, atheromatous diseases, diabetes mellitus, hyperglycemia, obesity, hyperlipidemia, hypertriglyveridemia, hypercholesteremia, raising HDL levels, atherosclerosis, vascular restinosis, irritable bowel syndrome, pancreatitis, abdominal obesity,

adipose cell tumors, adipose cell carcinomas, liposarcoma, disorders where insulin resistance is a component, Syndrome X, ovarian hyperandrogenism, obesity, hypoalphalipoproteinemia, type H diabetes, vascular disease, and skin wound healing.

59. A method for the treatment, prevention, or inhibition of Alzheimer's disease in a subject in need of such treatment, prevention, or inhibition, the method comprising treating the subject with a peroxisome proliferator-activated receptor-α agonist and a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.